HISTORY
The approach to both the history and physical examination of a child is often a collaborative effort that involves the child, her caregiver, and the provider. With a preverbal or very young patient, clinicians obtain the majority of the history from a parent or caregiver. Even for the very young patient, developmentally appropriate social questions directed to the patient can help. Gentle lateral traction on the labia majora usually allows complete visualization of the hymen and vaginal orifice. The hymen should be evaluated for patency. Most hymenal variations—imperforate, microperforate, septate—do not require treatment during the neonatal period. Variations should be noted and readdressed in subsequent visits. The hymen originates from the urogenital sinus. The uterus and vagina originate from the müllerian ducts. The concomitant renal malformations seen with müllerian anomalies are not associated with hymenal anomalies. Hymenal polyps seen in newborns typically regress in size as the maternal estrogen effects subside. Cervicovaginal mucus secretions can accumulate behind the blocked outflow tract of an imperforate hymen and manifest as a mucocolpos. In this instance, correction of the imperforate hymen in the neonatal period is indicated if urinary obstruction occurs.

The clitoris may appear large in proportion to the other genital structures, especially in premature infants. If the clitoris appears enlarged, the clitoral width should be measured; values >6 mm in a newborn indicate a need for further evaluation. If clitoromegaly and ambiguous genitalia are present, the obstetrician and pediatrician should immediately obtain expert consultation for evaluation of the infant and to counsel the parents. Congenital adrenal hyperplasia is the most common cause of ambiguous genitalia (accounting for more than 90% of cases), and the salt-wasting forms can lead to rapid dehydration with subsequent fluid and electrolyte imbalance (see Chapter 576). Delay in the diagnosis and treatment of congenital adrenal hyperplasia may be life-threatening.

In the neonate, the ovaries are <1 cm in diameter and average 1 cm³ in volume. Antenatal or postnatal abdominopelvic ultrasound might reveal small simple ovarian cysts, which represent normal follicles. Because of the abdominal location of ovaries in the neonate, ovarian enlargement can manifest as a palpable abdominal mass. Large cysts (>4-5 cm) or those of a complex nature pose the risk of ovarian torsion, hemorrhage into the cyst, or, uncommonly, an ovarian tumor. A non-resolving or enlarging neonatal ovarian cyst warrants expert consultation. If the mass causes respiratory compromise or gastrointestinal obstruction, decompression is usually performed. Cyst aspiration can give temporary relief, but it is not recommended as the fluid aspirated is not reliable for diagnosis and fluid may reaccumulate. If a cystectomy is done for appropriate clinical indications the cyst wall should be surgically excised to prevent reaccumulation of fluid and to provide a pathologic diagnosis, the remaining ovarian tissue should be left in situ, and the contralateral ovary should be inspected. Preservation of normal ovarian tissue is recommended for all benign lesions, and salpingo-oophorectomy should not be performed unless clinically indicated.

Neonates
The delivering obstetrician should briefly examine the external genitals of female infants to confirm the patency of the vagina and assess the presence of any obvious genital anomalies. The pediatrician’s newborn examination should note any abnormal findings such as ambiguous genitalia, imperforate hymen, urogenital abnormalities, abdominal mass, or inguinal hernia that might herald a gynecologic problem. Placing the infant in the supine position with thighs flexed against the abdomen allows visualization of the neonate’s external genitals. Estrogenic effects commonly notable in neonates include prominence of the labia majora and a white vaginal discharge. The labia minora and hymen may protrude slightly from the vestibule. A small amount of neonatal vaginal bleeding from endometrial sloughing following maternal hormone withdrawal might occur. Bleeding that is excessive or persistent beyond 1 mo of life requires further evaluation. Breast buds may be palpable at the time of the neonatal examination but should regress in the 1st mo of life; occasionally, nipple discharge occurs.

The vaginal orifice may be difficult to see. Gentle lateral traction on the labia majora usually allows complete visualization of the hymen and vaginal orifice. The hymen should be evaluated for patency. Most hymenal variations—imperforate, microperforate, septate—do not require treatment during the neonatal period. Variations should be noted and readdressed in subsequent visits. The hymen originates from the urogenital sinus. The uterus and vagina originate from the müllerian ducts. The concomitant renal malformations seen with müllerian anomalies are not associated with hymenal anomalies. Hymenal polyps seen in newborns typically regress in size as the maternal estrogen effects subside. Cervicovaginal mucus secretions can accumulate behind the blocked outflow tract of an imperforate hymen and manifest as a mucocolpos. In this instance, correction of the imperforate hymen in the neonatal period is indicated if urinary obstruction occurs.

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As puberty approaches, the child experiences increasing endocrine activity of the hypothalamus, pituitary gland, adrenal gland, and ovaries (see Chapter 561). The labia majora begin to fill out, and the labia minora thicken and elongate as a result of increased estrogen levels. The hymen thickens and becomes more redundant. Clear or white physiologic secretions may be present. Breast buds begin to appear, either bilateral or initially unilateral with subsequent development of the contralateral breast.

Indications for Genital Examination
Genitourinary complaints or suspected genitourinary pathology warrant assessment of the external and internal genitals of pediatric patients, specifically in cases of vaginal bleeding, vaginal discharge, vulvar trauma, presence of a foreign body, perineal or pelvic masses, vulvovaginal ulcerative or inflammatory lesions, congenital anomalies, or suspected sexual abuse.

Preparation
The genital examination in prepubertal girls requires a gentle, patient approach to maximize cooperation and minimize fear and embarrassment. A clear, simple explanation of what the exam involves can facilitate the child's comfort and cooperation. The presence of a parent or caregiver during the entire examination provides reassurance for most children. For the older prepubertal patient, the physician may discuss whether the patient wishes to have a family member present during the examination. Even in the presence of the caregiver, the examiner should speak directly to the child. Prior to initiating any part of the examination, the provider should explicitly verify with both the patient and her caregiver that the caregiver has given permission for the examination. This provides an opportunity to explain to the child the privacy of body parts and who may examine or touch those areas. It is useful to educate the patient and caregiver about the basic anatomy and hygiene of the external genital area. Before each step of the examination, the physician should explain what will occur. Allowing an older child the option of watching her examination with a handheld mirror may contribute to her comfort and understanding. Forcible restraint is never indicated; if optimal evaluation is not possible, the clinician must assess the acuity of the complaint and pathology and determine the potential need for a multi-visit examination or an examination under anesthesia.

Positioning
A variety of techniques and positions can facilitate the genital examination in prepubertal patients. Children younger than 4 yr of age can be placed on the parent or caregiver's lap with the child's legs straddling the parent's thighs. If the child permits, she may be positioned on the table in the supine position with the hips fully abducted and the feet together in the frogleg (diamond or butterfly) position. Older children may prefer to use the stirrups. The head of the examination table should be raised so that eye contact can be maintained with the patient throughout the examination. When the child is supine, grasping the labia majora along the inferior portion between the thumb and index finger and gently pulling outward and posteriorly (labial traction) allows visualization of the vaginal introitus. Alternatively, the child may be placed in the knee–chest position with elevation of the buttocks and hips. This position provides exposure of the inferior portion of the hymen, the lower vagina, and possibly the upper vagina and cervix but has the disadvantage of having the child face away from the examiner.

Some extremely cooperative children tolerate a vaginoscopic examination in an outpatient office setting for better intravaginal assessment. The endoscope (either a cystoscope or a hysteroscope) is placed in the vagina and the labia are gently opposed, allowing the vagina to distend with water. This technique permits visualization of the vagina and cervix, allowing for the evaluation of an injury, lesion, and anatomic variant or for the presence of a foreign body. Application of 2% lidocaine gel at the introitus makes the insertion easier and less irritating for the patient. If a more complete examination is indicated or if the child is too young, frightened or unable to cooperate, an examination under anesthesia is recommended.

Documentation
Clinicians should thoroughly and accurately document genital exam findings in the medical record, reserving conclusions and diagnostic terms for the impression and plan portion of the documentation rather than in the description of exam findings. Each structure visualized should be noted (e.g., clitoris, labia majora, labia minora, urethra, vestibule, and rectum) with attention to describing normal appearance and any anatomic variations (e.g., the configuration of the hymen as annular, crescentic, etc.). Describing any findings or lesions using a clock-face method provides a consistent reference point; a sketch or magnified photograph may also be helpful. Future examiners will rely on this documentation as a record with which they compare their findings and note any variances. Changes should be noted in any follow-up examinations.

Adolescents
Some teens prefer to initially meet and discuss the reason for their visit with the provider without their parent or guardian present, and this request should be honored (see Chapter 112). A majority of the time, obtaining a history from an adolescent begins with meeting the patient and her parent or caregiver together to review her history and the reason for the visit and to explain the concepts of confidentiality and privacy. Familiarity with local laws governing limitations to confidential services should guide the protection of the adolescent and her parents’ rights to information access and privacy. The Guttmacher Institute provides an up-to-date listing of state and federal laws in the United States affecting access to medical care (http://www.guttmacher.org/statecenter/spibs/spibs/index.html). Brief discussions of normal pubertal development and menstruation can reassure both patients and their parents or guardians and provide valuable education on appropriate menstrual flow, menstrual hygiene and the duration and frequency of bleeding. Introducing the menstrual diary as an invaluable tool for the teen can help patients, parents, and clinicians identify abnormal bleeding patterns that might require further evaluation. Many apps are available for tracking menstrual periods on a smartphone or computer.

After the initial interview with the teen and her parent or caregiver, the confidential and sensitive portion of the history, particularly sexual history and alcohol, tobacco, and drug use, is taken with the teen alone. Such a request could be phrased as follows: “I would like to give your daughter an opportunity to ask any questions she might have privately, so would you mind stepping out of the room for a moment?” Concerns for the presence of vaginal discharge, the potential for sexually transmitted infections, pregnancy, or menstrual aberration should be explored. Teens and their parents should be informed of the proper use and accessibility of condoms, all contraceptive methods, and emergency contraception.

A number of resources for educating adolescents regarding their first pelvic examination and in-depth sexual history and psychosocial screening tools are available. These include the North American Society for Pediatric and Adolescent Gynecology (http://www.naspag.org), the American Academy of Pediatrics (http://www.aap.org), the Society for Adolescent Health and Medicine (http://www.adolescenthealth.org), and the American College of Obstetricians and Gynecologists (http://acog.org/Patients).

Pelvic Examination
Table 548-1 presents the indications for the first pelvic examination in adolescents: age older than 21 yr, abnormal uterine bleeding, vulvo-vaginitis, severe dysmenorrhea, unexplained dysuria or abdominal pain, evaluation and removal of a foreign body, and placement of an intrauterine device. If an adolescent does not meet 1 of the criteria
Before touching the introitus, it may be useful to touch the inner thigh with the speculum. Compression of the urethra anteriorly should be avoided. Gentle pressure with a finger for displacement of the fourchette posteriorly further facilitates proper speculum placement. After visualization of the vagina and cervix, specimens should be obtained as indicated. A bimanual examination, sometimes with a single digit, allows palpation of the vaginal walls and cervix and bimanual assessment of the uterus and adnexa. Reassurance of normal findings throughout the examination should be provided, and normal variants to anatomy should be pointed out to the teen as they are encountered (e.g., asymmetric labia minora).

Following the examination, it is appropriate to review the exam findings with the teen (and her parent) and initiate a collaborative discussion of the management plan. Encouraging the adolescent to participate in decision making empowers her to undertake responsibility for her health, may strengthen compliance with the medical plan, and acknowledge her as a unique individual.

Bibliography is available at Expert Consult.

listed in Table 548-1, the American College of Obstetricians and Gynecologists recommends that the first gynecologic encounter occur between the ages of 13 and 15 yr (Table 548-2) with attention toward anticipatory guidance focusing on normal pubertal development and menstruation. Patients should undergo screening for sexually transmitted infection with each new sexual partner. With the availability of urine and vaginal swab nucleic acid amplification testing for chlamydia and gonorrhea, sexually transmitted infection screening does not necessitate a speculum exam.

Prior to the initiation of a physical examination, all young women should be offered the choice of having a medical attendant, family member, or friend present during her examination. At the initial gynecologic exam, the physician should explain the process in understandable terms. A thorough evaluation begins with an assessment of body mass index, blood pressure, menstruation status, thyroid, lymph nodes, breast development, abdominal exam, and skin. The external genitals should be examined with the patient in the dorsal lithotomy position while communication is maintained between the physician and patient. Elevating the head of the examination table allows the teen and her examiner to maintain eye contact. The teen can hold a mirror to follow along with the examination, and she should be encouraged to ask questions. Inspection of the vulva is followed by inspection of the Bartholin, urethral, and Skene glands. The clitoris, normally 2-4 mm in width, is then assessed; a clitoris wider than 10 mm, especially in the presence of other signs of virilization, suggests a need for further evaluation. The hymenal anatomy should also be evaluated. Throughout the examination, the proper nomenclature for genital anatomy should be emphasized with the teen to empower her to use proper wordage with the avoidance of slang when referring to her body.

Because the initial Papanicolaou test is deferred until 21 yr of age and cultures for sexually transmitted infections can be obtained from urine or vaginal swabs, the need for a speculum exam is decreasing in this age group. If a speculum exam is indicated, use an appropriate sized speculum, such as the Huffman (⅜ in wide × 4 in long) or Pedersen (Ⅲ in wide × 4 in long). Shorter speculums will not allow visualization of the entire vaginal canal. The adolescent patient should be reassured that the exam may be uncomfortable but should not be painful and that her request to stop or wait will be honored. Encouraging the patient to watch with a hand-held mirror facilitates patient education and can be empowering. She may be told before the insertion of the speculum that she will experience a pressure sensation.
Bibliography


Committee on Adolescent Health Care: Tool kit for teen care, ed 2, Atlanta, 2009, American College of Obstetrician and Gynecologists.


Vulvovaginitis, the most common gynecologic-based problem for prepubertal children, is typically caused by either inadequate or excessive hygiene or chemical irritants. The condition is usually improved by hygiene measures and education of the caregivers and child.

**ETIOLOGY**

Vulvitis refers to external genital pruritus, burning, redness, or rash. Vaginitis implies inflammation of the vagina, which can manifest as a discharge with or without an odor or bleeding. These may occur simultaneously as vulvovaginitis. When a child presents with vulvovaginitis, the history should include questions on hygiene (wiping from front to back) and information about possible chemical irritants (bath soaps, laundry detergents, swimming pools, or hot tubs). The caregiver can be asked about a history of diarrhea, perianal itching, or nighttime itching. The possibility of foreign objects being placed into the vagina should also be asked, although the young child is unlikely to remember or recall. Children are especially prone to nonspecific vulvovaginitis for a variety of reasons, including their nonestrogenized state, poor perianal hygiene, and the proximity of the anus to the vagina, which is without geographic barriers given the flattened labia and lack of pubic hair (Fig. 549-1 and Table 549-1).

**EPIDEMIOLOGY**

Infectious vulvovaginitis, where a specific pathogen is isolated as the cause of symptoms, may be caused by fecal or respiratory pathogens and cultures might reveal *Escherichia coli* (see Chapter 200), *Streptococcus pyogenes*, *Staphylococcus aureus* (see Chapter 181), *Haemophilus influenzae* (see Chapter 194), *Enterobius vermicularis*, and, rarely, *Candida* spp. (see Chapter 234). These organisms may be transmitted by the child using improper toilet hygiene and manually from the nasopharynx to the vagina. The children present with perianal redness, an inflamed introitus, and often a yellow-green or mildly bloody discharge. They may be observed to be grabbing their genital area or “digging” in their underwear, which is usually stained with yellow-brown discharge. Attempts to treat these bacterial etiologies with antifungal medication will fail and often the antifungal product will lead to more irritation. Table 549-2 gives specific treatment recommendations based on the bacteria localized.
Neisseria gonorrhoeae or Chlamydia trachomatis also are causes of specific infectious vulvovaginitis (see Chapter 120). Management of children who have sexually transmitted infections requires close cooperation between clinicians and child-protection authorities. Official investigations for sexual abuse, when indicated, should be initiated promptly (see Chapter 40). If acquired after the neonatal period, some diseases (e.g., gonorrhea, syphilis, and chlamydia) are virtually 100% indicative of sexual contact. For other diseases (e.g., human papillomavirus infection and herpes simplex virus), the association with sexual contact is not as clear. Presumptive treatment for children who have been sexually assaulted or abused is not recommended because (1) the incidence of most sexually transmitted infections in children is low after abuse/assault, (2) prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and (3) regular follow-up of children usually can be ensured. Although Trichomonas vaginalis can be transmitted vertically and can be seen in children up to 1 yr of age, it is an uncommon cause of specific infectious vulvovaginitis in the unestrogenized prepubertal girl.

Other causes of specific infectious vulvovaginitis include Shigella (see Chapter 199), which often manifests with a blood-tinged purulent discharge, and Yersinia enterocolitica (see Chapter 203). Candida infections (yeast) commonly cause diaper rash, but they are unlikely to cause vaginitis in children because the alkaline pH of the prepubertal vagina does not support fungal infections. Exceptions can occur in diabetic or immunocompromised children or children on prolonged antibiotics. Pinworms are the most common helminthic infestation in the United States, with the highest rates in school-age and preschool children. Perianal itching can lead to excoriation and, rarely, bleeding.

**CLINICAL MANIFESTATIONS**

**Diaper Dermatitis**

Diaper dermatitis is the most common dermatologic problem in infancy and occurs in half of all diaper-wearing infants and children. The moisture and contact with urine and feces irritate the skin, and colonization with Candida spp. increases the severity of the dermatitis. First-line treatment includes hygiene measures such as increasing the frequency of diaper changes, allowing the infant to be diaper free,

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### Table 549-1: Specific Vulvar Disorders in Children

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<tr>
<th>ORGANISM</th>
<th>PRESENTATION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
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</table>
| Molluscum contagiosum (Fig. 549-7)| 1-5 mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug | Diagnosis usually is made by visual inspection | The disease generally is self-limited and the lesions can resolve spontaneously  
  Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curstead, podophyllotoxin, and topical silver nitrate  
  Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects |
| Condyloma acuminata                | Skin-colored papules, some with a shaggy, cauliflower-like appearance | Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question. Human papillomavirus DNA testing is not helpful | Many lesions in children resolve spontaneously, “wait and see” often utilized in children (60 days). Topical treatment with imiquimod cream and podophyllotoxin is the most studied (daily qhs 3 times/wk x 16 wk, wash 6-10 hr after application). General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery)–reserve for symptomatic or large lesions. Other treatments have been utilized in adults, including trichloroacetic acid, 5-fluorouracil, sinecatechins, topical cidofovir, and cimetidine. The efficacy and safety of these treatments in children has not been established |
| Herpes simplex                    | Blisters that break, leaving tender ulcers         | Visual inspection confirmed by culture from lesion | Infants: Acyclovir 20 mg/kg body weight IV q8h x 21 days for disseminated and central nervous system disease or x 14 days for disease limited to the skin and mucous membranes  
  Genital/mucocutaneous disease:  
  Age 3 mo–2 yr: 15 mg/kg/day IV divided in q8h x 5-7 days  
  Age 2-12 yr (1st episode): Same as above or 1,200 mg/day divided in q8h dosing x 7-10 days  
  Age 2-12 yr (Reoccurrence): 1,200 mg/day in q8h dosing or 1,600 mg/day in bid dosing x 5 days (give 3-5 days for children older than 12 yr) |
### Table 549-1  Specific Vulvar Disorders in Children—cont’d

<table>
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<tr>
<th>ORGANISM</th>
<th>PRESENTATION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
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| Labial agglutination      | May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis | Diagnosis is made by visual inspection of the adherent labia, often with a central semitranslucent line | Does not require treatment if the patient is asymptomatic  
Symptomatic patients: Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction  
Estrogen should be interrupted if breast budding occurs  
Mechanical or surgical separation of the adhesions is rarely indicated  
The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, reoccurrence is common  
To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime |
| Lichen sclerosus          | A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin, subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma  
The patient can experience perineal itching, soreness, or dysuria | Diagnosis usually is made by visual inspection  
Biopsy should be reserved for when the diagnosis is in question | Ultrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk  
Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up  
In many girls, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up |
| Psoriasis                 | Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetrical plaques. The classic extragenital lesion are similar but with a silver scaly appearance | Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears | Vulvar lesions may be treated with low to medium potency topical corticosteroids, increasing strength as necessary |
| Atopic dermatitis         | Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema  
Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection | It may be seen in the vulvar area but characteristically affects the face, neck, chest, and extremities | Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups  
If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing |
| Contact dermatitis        | Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed | Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components | Avoidance of irritant  
Topical corticosteroids for flare-ups |
| Seborrheic dermatitis     | Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face | Diagnosis usually is made by visual inspection | Gentle cleaning, topical clotrimazole with 1% hydrocortisone added |
| Vitiligo (Fig. 549-5)     | Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions. May be present in periphery at body orifices and extensor surfaces | Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus) | If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions |
Genital Ulcers

Acute genital ulceration of the vulva (Fig. 549-2) is described in young adolescents who are not sexually active and can occur in association with oral aphthous ulcers. Although linked to infectious causes such as Epstein-Barr, cytomegalovirus, mycoplasma, and influenza A, recent data suggest these ulcers may be idiopathic vulvar aphthoses.

**Physiologic Leukorrhea**

Neonates and peripubertal girls can present with a white or clear or mucus discharge, which is a physiologic effect of estrogen. Some girls complain of the moisture and mucus, but an explanation should reassure the patient and her mother.

**Genital Ulcers**

Acute genital ulceration of the vulva (Fig. 549-2) is described in young adolescents who are not sexually active and can occur in association with oral aphthous ulcers. Although linked to infectious causes such as Epstein-Barr, cytomegalovirus, mycoplasma, and influenza A, recent data suggest these ulcers may be idiopathic vulvar aphthoses.

Other potential etiologies include inflammatory bowel disease, Behçet disease, pemphigoid, Stevens-Johnson syndrome, drug eruption, or mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome.

These lesions usually appear on the mucosal surfaces of the introitus as painful red or white lesions that evolve into sharply demarcated red-rimmed ulcers with a necrotic or eschar-like base. The time course is generally 10-14 days until remission occurs. The lesions are quite painful and pain management and urinary diversion with a Foley catheter may be necessary. Patients with acute genital ulcers show a fairly consistent picture of flu-like prodromal symptoms, dysuria, and
vulvar pain. One-third of patients present with a history of or develop oral ulcerations. Evaluation includes culture for herpes simplex virus to exclude this etiology. Special testing for systemic disease depends on history. Biopsies are usually nondiagnostic as they yield acute and chronic inflammatory changes. Figure 549-3 outlines suggested evaluation and management for initial and recurrent disease. Evaluation for Behçet disease (see Chapter 161) using the International Study Group diagnostic guidelines should be considered with recurrent or severe cases. (See Table 549-1 for other common etiologies.) Treatment of acute genital ulcers should include topical Xylocaine 2% jelly, sitz baths, good hygiene, and acetaminophen. Nonsteroidal antiinflammatory drug avoidance is suggested because of a possible causative link. Hospitalization may be required for pain management not controlled with oral narcotics, urinary retention requiring Foley catheterization or for whirlpool debridement should hygiene become difficult. Antibiotic treatment is not required unless evidence of bacterial superinfection exists or the patient is immunocompromised. Insufficient evidence exists to recommend whether oral steroid treatment is effective but may be helpful in the setting of recurrent outbreaks. Ultrapotent topical steroids (clobetasol 0.05% ointment), however, are beneficial in oral aphthous ulcers and may prove helpful in acute genital ulcers as well.

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**Figure 549-2** Aphthous ulcers. (Photo courtesy of Diane F. Merritt, MD.)

Dermatologic conditions often affect the vulvar area in children; it is important to determine if the girl presenting with vulvar irritation has a skin condition elsewhere on the body. Lichen sclerosus is commonly seen in the anogenital region and has a characteristic appearance of white skin changes associated with areas of erosion, ulceration, and petechia. This disease can cause severe discomfort and most commonly presents with vulvar or perianal pruritus, dysuria, and constipation. Patients may also present without any symptoms, which may lead to underrecognition and under treatment. If untreated, lichen sclerosus can lead to destruction and scarring of normal genital architecture, including labial resorption, obliteration of the clitoris, narrowing of the introitus, and painful fissures that may become secondarily infected. Once thought to resolve with puberty, this theory is now controversial and many postmenarchal adolescents still suffer from disease. Any time a young female presents with vulvar irritation, the clinician should strongly consider lichen sclerosus. Lichen sclerosus may be treated with potent topical steroids, clobetasol propionate 0.05% applied once or twice daily until the symptoms resolve.

Vitiligo is an acquired skin depigmentation resulting from an autoimmune process directed at epidermal melanocytes. Lesions appear as sharply demarcated patches of pigment loss, often symmetrically located around vagina and anal area. Similar lesions of hypopigmentation can be found surrounding body orifices and extensor surfaces (Fig. 549-5). Although diagnosis is clinical, there is an association with other autoimmune or endocrine disorders (hypothyroidism, Graves disease, Addison disease, pernicious anemia, insulin-dependent diabetes mellitus) and workup should include evaluation for at least thyroid dysfunction. Mild topical corticosteroid cream or ointment may be prescribed for children. Dermatologists may offer immunomodulators (tacrolimus), and phototherapy.

Vulvar psoriasis presents as pruritic, well-demarcated nonscaly, erythematous, symmetrical plaques that involve the vulva, perineum and/ or gluteal folds. Lesions on the mons pubis may have the more characteristic scaly appearance. The classic signs of psoriasis may also be appreciated with pitting nail beds, posterior auricular erythema or a silvery scaling rash found elsewhere on the body. Many of the treatments used in adults may not be appropriate in children. Psoriasis may be treated with moisturizers, topical steroids, and light therapy. Teens may be treated with coal tar, retinoids, tacrolimus, and calcipotriene, which is a derivative of vitamin D3.

TREATMENT AND PREVENTION

The treatment of specific vulvovaginitis should be directed at the organism causing the symptoms (see Table 549-1). Treatment of non-specific vulvovaginitis includes sitz baths and avoidance of irritating or harsh soaps and chemicals and tight clothing that abrades the perineum. External application of bland emollient barriers such as nonprescription diaper rash medications and petroleum jelly may be helpful. Proper perineal hygiene is critical for long-term improvement. Younger children need supervised perineal hygiene, and caregivers should be advised to wipe the genital area from front to back. Use of a warm moistened washcloth or diaper wipe is helpful after initially wiping with toilet tissue. Girls should wear cotton underwear and limit time spent in tights, leotards, jeggings, tight jeans, and wet swimsuits. Soaking in warm clean bathwater for 15 min intervals (no shampoo or

**Dermatoses**

Dermatologic conditions often affect the vulvar area in children; it is important to determine if the girl presenting with vulvar irritation has a skin condition elsewhere on the body. Lichen sclerosus is commonly seen in the anogenital region and has a characteristic appearance of white skin changes associated with areas of erosion, ulceration, and petechia. This disease can cause severe discomfort and most commonly presents with vulvar or perianal pruritus, dysuria, and constipation. Patients may also present without any symptoms, which may lead to underrecognition and under treatment. If untreated, lichen sclerosus can lead to destruction and scarring of normal genital architecture, including labial resorption, obliteration of the clitoris, narrowing of the introitus, and painful fissures that may become secondarily infected. Once thought to resolve with puberty, this theory is now controversial and many postmenarchal adolescents still suffer from disease (Fig. 549-4). Lichen sclerosis may be treated with potent topical steroids, clobetasol propionate 0.05% applied once or twice daily until the symptoms resolve.

Vitiligo is an acquired skin depigmentation resulting from an auto-immune process directed at epidermal melanocytes. Lesions appear as sharply demarcated patches of pigment loss, often symmetrically located around vagina and anal area. Similar lesions of hypopigmentation can be found surrounding body orifices and extensor surfaces (Fig. 549-5). Although diagnosis is clinical, there is an association with other autoimmune or endocrine disorders (hypothyroidism, Graves disease, Addison disease, pernicious anemia, insulin-dependent diabetes mellitus) and workup should include evaluation for at least thyroid dysfunction. Mild topical corticosteroid cream or ointment may be prescribed for children. Dermatologists may offer immunomodulators (tacrolimus), and phototherapy.

Vulvar psoriasis presents as pruritic, well-demarcated nonscaly, erythematous, symmetrical plaques that involve the vulva, perineum and/ or gluteal folds. Lesions on the mons pubis may have the more characteristic scaly appearance. The classic signs of psoriasis may also be appreciated with pitting nail beds, posterior auricular erythema or a silvery scaling rash found elsewhere on the body. Many of the treatments used in adults may not be appropriate in children. Psoriasis may be treated with moisturizers, topical steroids, and light therapy. Teens may be treated with coal tar, retinoids, tacrolimus, and calcipotriene, which is a derivative of vitamin D3.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Children with symptoms of vulvovaginitis often have had a previous evaluations and treatment failures. Cultures with sensitivities to test for specific pathogens may be obtained with cotton swabs or urethral (Calgiswab) swabs moistened with nonbacteriostatic saline. Use of a swab can cause discomfort or, rarely, minimal bleeding. The premoistened swab can be placed vertically between the labia minora to collect secretions, as it is not necessary to place the swab into the vagina. Testing for gonorrhea and chlamydia may be done by culture or by nucleic acid amplification testing, depending on institutional or state and Centers for Disease Control guidelines. Tests for Shigella and H. influenzae might require special media and collection procedures.

If pinworms (see Chapter 294) are suspected, transparent adhesive tape or an anal swab should be applied to the anal region in the morning before defecation or bathing and then placed on a slide. Eggs seen on microscopic examination confirm the diagnosis, and sometimes the pinworms can be seen at the anal verge. Clinical history is often more indicative of disease than physical exam, and a negative tape test does not rule out this pathogen as a cause.

If the vaginal discharge is serosanguineous, if a foul odor is present, or if the discharge fails to respond to hygiene measures, consider presence of a vaginal foreign body (Fig. 549-6). If inspection suggests presence of a foreign body, the vagina can be irrigated, or an examination under anesthesia may reveal the foreign body. Vaginoscopy is an excellent diagnostic tool and can be performed in an unsedated cooperative patient in an outpatient setting, or under general anesthesia if necessary. Using a cystoscope with saline or water irrigation to gravity, insert the endoscopic device into the vagina, gently oppose the labia, the vagina will distend and the entire vaginal cavity and cervix may be easily assessed.

**Figure 549-4 Lichen sclerosus. (Photo courtesy of Diane F. Merritt, MD.)**

**Figure 549-5 Vitiligo. (Photo courtesy of Diane F. Merritt, MD.)**
bubble bath) is soothing and helps with cleaning the area. Parents should be counseled to avoid all scented, antiseptic, and deodorant-based soaps, and to eliminate the use of fabric softeners or dryer sheets when laundering undergarments.

Bibliography is available at Expert Consult.
Chapter 549  Vulvovaginitis  2613.e1

Bibliography
Vaginal bleeding in infants and prepubescent children should always be evaluated. Bleeding can be seen as early as the 1st wk of life, resulting from endometrial sloughing associated with maternal estrogen withdrawal. A thorough history and physical must be obtained as the 1st step in evaluating the problem. Common causes for vaginal bleeding include neoplasms and trauma.

Vulvovaginitis (see Chapter 549) may be caused by respiratory, oral and fecal pathogens, some of which produce serosanguineous drainage (e.g., *Streptococcus, Shigella*) or cause vulvar bleeding resulting from irritation and excoriation of the skin. Prepubertal girls are at a higher risk for developing these irritations because the protective labia of pubertal girls are not fully developed and thus, the vaginal opening and vagina are easily more exposed to irritants. Further, the hypoestrogenic vaginal mucosa is thin and lacks the protective effects of an acidic pH from lactobacilli. The alkaline vaginal pH noted in prepubertal girls results in an environment more prone to infection. Hand-washing, improved perineal hygiene (wiping front to back, use of wet wipes after bowel movement), and avoidance of topical irritants, chemicals, and perfumed or deodorant soaps and bubble baths will reduce nonspecific vulvovaginitis. External application of bland emollient barriers such as over the counter diaper rash ointments or petroleum jelly may be helpful (see Table 549-2 in Chapter 549). Antibiotics will help with recurrent or persistent infections if a specific pathogen is identified by culture.

Hematuria is suspected when the urine is red or brown. Gross hematuria may be confused with vaginal bleeding. A positive urinary dipstick can confirm blood, but pigments and metabolites may also cause red or brown urine (see Chapter 509). The cause of gross hematuria in symptomatic children is usually elicited by a complete history, physical examination and urinalysis. Additional diagnostic studies may include ultrasound of the kidneys and bladder, urine culture, measurements of urine calcium/creatinine, and serum C3 and creatinine. Treatment depends on the diagnosis.

Dermatoses may present with bleeding. Lichen sclerosus (see Fig. 549-4 and Table 549-1 in Chapter 549) is characterized by chronic inflammation, intense pruritus, loss of normal architecture, thinning and whitening of the vulvar and perianal skin often in a butterfly or keyhole distribution. Petechiae or blood blisters can arise and be mistaken as a sign of sexual abuse. Diagnosis is based on these classic clinical characteristics, but may be confirmed by a tissue biopsy if necessary. As a first-line treatment, potent topical steroids, such as clobetasol propionate ointment 0.05%, may be applied sparingly to the affected tissue 1-2 times a day under physician supervision; they usually result in improvements in appearance and pruritus. The steroid should be used for the shortest duration necessary then be stopped or tapered. Flare-ups can occur and require retreatment.

Foreign bodies are a common cause of vaginal bleeding, and children present with blood-stained and foul-smelling discharge. The most common object found in prepubertal girls is toilet paper. A physical exam in knee–chest or frogleg position can sometimes reveal the object. Vaginal irrigation may be done in the office setting using a small feeding tube, a syringe, and warm water. If the object is not visible on examination, irrigation is unlikely to remove it and examination under anesthesia and vaginoscopy are often required. Vaginoscopy not only allows removal of a foreign object but also can facilitate diagnosis of other causes of the bleeding.

Trauma to the vulva or vagina is especially concerning. Most of these injuries are accidental, but physical and sexual abuse must be ruled out (see Chapter 40). Straddle injuries such as falling on the cross bar of a bicycle or slipping in the bathtub may result in bruising, hematomas, and lacerations. In general, if the trauma is accidental, the hymen and vagina are spared as most accidental injuries involve the mons and labia. If there are no eyewitnesses to the injury, if there is no history to explain the clinical findings, and especially if there is a laceration of the hymen, abuse must be considered in the differential diagnosis, and a forensic interview of the patient and family should take place. If the injury is penetrating, further examination and imaging are necessary to evaluate the urethra, bladder, anus, and intraabdominal structures. General anesthesia may be needed to fully assess injuries and allow adequate repair; while minor lacerations may be repaired in a cooperative child under sedation or local anesthesia. If the patient is able to
void spontaneously, nonexpanding hematomas can be observed and treated with ice, pressure, and pain medications. Large expanding hematomas should be carefully evaluated and may require drainage, ligation of the bleeding vessels, and/or placement of a closed suction drain, especially if the overlying skin is showing signs of necrosis. A Foley catheter should be placed for children who are having difficulty with voiding.

Urethral prolapse (see Chapter 544) is another potential cause of bleeding in the prepubertal girl. The patient may present with a circular protrusion of the urethral mucosa through the external meatus forming a friable vulvar mass. Downward traction at the introitus enables visualization of the vaginal orifice separate from the urethral mass and assists with confirming the correct diagnosis. Patients may be asymptomatic or present with bleeding, dysuria, or difficulty with urination. Low estrogen state, trauma, chronic cough, and constipation are believed to be predisposing factors. Treatment is conservative, with application of estrogen cream at the area of prolapse twice daily for 1-2 wk and then, if prolapse is still present, continued use until the prolapse resolves. Surgical excision is very rarely necessary to remove necrotic tissue.

Neoplasms of the vulva and vagina are rare (see Chapter 553). Infantile hemangiomas are the most common benign vascular neoplasm of infancy, affecting 5% of all infants. Most lesions proliferate then involute, and only a few require intervention. Hemangiomas of the perineum may be associated with spinal dysraphism, so a neurologic assessment should be performed. Intralesional and systemic steroids have been used to treat infantile hemangiomas. Propranolol therapy results in a good response rate. Laser therapy and surgical excision are sometimes used.

Like hemangiomas, hymenal polyps are usually benign. If these polyps are noted at birth, they generally regress after maternal levels of estrogen decrease in the infant. If hymenal polyps persist, grow, or cause discomfort they may be removed. Vaginal polyps, especially if they cause bleeding, should be removed (not followed) and sent for pathologic evaluation. Yolk sac (endodermal sinus) tumors of the vagina are rare but may cause vaginal bleeding. Serum α-fetoprotein is a reliable marker. Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood. In children, the most common sites are the head and neck (35%) and genitourinary region (25%) (see Chapter 500). Rhabdomyosarcoma arising in the genitourinary tract are commonly the sarcoma botryoides variant and are typically seen in the 1st decade, often before age 3 yr, and present with vaginal discharge and bleeding. Treatment consists of a multimodal approach, including surgery, radiation therapy, and chemotherapy. The survival rate is >90% when an early diagnosis is made.

Vaginal bleeding can be a presenting sign of precocious puberty, which is defined as pubertal development that is 2.5-3.0 SD earlier than the average age. Guidelines for the evaluation of premature development state that pubic hair or breast development requires evaluation generally when it occurs before age 7 yr in non–African-American girls and before age 6 yr in African-American girls (see Chapters 561 and 562). Rapidity of pubertal progression, such as Tanner stage 3 breast development before 8 yr of age, may also require evaluation. The most common etiology is gonadotropin-dependent or central precocious puberty (see Chapter 562.1) where there is premature enhancement of pulsatile gonadotropin-releasing hormone release resulting in ovarian follicle growth and estrogen production. Gonadotropin-independent precocious puberty, where estrogen production is not under hypothalamic control and is produced peripherally, such as from an ovarian/adrenal tumor or McCune Albright syndrome, is less common.

A thorough physical exam must be done, looking for secondary sex characteristics and documenting breast and pubic hair development using the Sexual Maturation Index (Tanner Staging; see Chapter 110.1). Documenting height and weight on a growth chart will assist in identifying accelerated growth velocity. Diagnostic tests include a left wrist x-ray to look for advanced bone age. Elevated serum luteinizing hormone levels are highly suggestive of central precocity, but the gold standard is measurement of gonadotropins after gonadotropin-releasing hormone or gonadotropin-releasing hormone–agonist stimulation. In all cases of central precocious puberty, MRI imaging of the brain is needed to determine if a tumor is present. Pelvic ultrasound might show presence of ovarian or adrenal pathology or uterine maturation in response to estrogen. Benign premature ovarian follicles or malignant ovarian germ cell tumors can produce elevated serum estradiol levels >100 pg/mL. If the estradiol is elevated, pelvic imaging by transabdominal ultrasound is mandated. Usually benign ovarian follicles produce short periods of estrogen elevation which is enough to stimulate the endometrial lining and result in endometrial shedding. Usually by the time the pelvic ultrasound is obtained the follicular structure has collapsed and resolved and the estrogen level has dropped to prepubertal range. If indicated central precocious puberty can be suppressed with leuprolide injections or histrelin implants. Germ cell tumors are treated by excision, staging and chemotherapy by protocols provided by oncologists.

Juvenile hypothyroidism commonly causes pubertal delay. Patients with severe, long-standing and untreated hypothyroidism may present with premature breast development, vaginal bleeding and abdominal distention resulting from ovarian enlargement and possibly ascites associated with deceleration of linear growth. A proposed mechanism is thyroid-releasing hormone–associated elevations of thyroid-stimulating hormone crossreacting with follicle-stimulating hormone resulting in follicle maturation and estradiol production. Treatment of the hypothyroidism results in improvement and reversal of symptoms.

Another etiology for childhood vaginal bleeding is exogenous exposures to estrogens. These exposures can occur from ingestion of birth control pills, foods, beauty products, and plastics that contain estrogen or estrogen-like components. Several other studies have assessed the risk of bisphenol A leaching from plastic cups and bottles. The importance of this is still being studied, but bisphenol A is known to have an estrogenic effect and thus could potentially be a cause for vaginal bleeding if ingested in high levels.

Vaginal bleeding in the prepubertal girl or infant can have many causes, which range from benign to malignant. A thoughtful history and physical examination must be done to identify the source of bleeding so that treatment can occur. The risk benefit of any therapy should be reviewed carefully with the family.

Bibliography is available at Expert Consult.
Bibliography
Presenting concerns of girls with breast disorders typically including the development or appearance of their breasts, breast pain, nipple discharge, or concerns about the presence of a mass. Although children and adolescents are very unlikely to have malignant or life-threatening breast problems, this population of patients should be referred to practitioners who have experience and familiarity with the immature and developing breast to avoid overtreatment with unnecessary diagnostic or surgical procedures.

BREAST DEVELOPMENT
Development of the breast begins around wk 5 of gestation, when the ectoderm on the anterior body wall thickens into 2 ridges known as the mammary ridges. They extend from the area of the developing axilla to the area of the developing inguinal canal. The ridge above and below the area of the pectoralis muscle recedes in utero, leaving the mammary primordium, which is the origin of the lactiferous ducts.
The initial lactiferous ducts form between wk 10 and 20 and become interspersed through the developing mesenchyme, which becomes the fibrous and fatty portions of the breast. The breast bud, under the stimulation of maternal estrogen, becomes palpable at wk 34 of gestation. This breast bud regresses within the 1st mo of life, because the estrogen stimulation is no longer present. The areola appears at 5 mo of gestation, and the nipple is seen shortly after birth. It is initially depressed and later becomes elevated.

**Thelarche**, or the onset of pubertal breast development, is hormonally mediated and normally occurs between the ages of 8 and 13 yr, with an average age of 10.3 yr. The initiation of thelarche and progression in females is affected by race, with normal thelarche occurring earlier in African-American girls than in white or Asian girls. This occurs when the hypothalamus releases gonadotropin-releasing hormone, which stimulates the pituitary gland to produce follicle-stimulating hormone and luteinizing hormone, which then stimulates the ovaries to produce estrogen. The estrogen leads to breast development.

Once thelarche is initiated, normal development of the breast occurs over 2-4 yr and is classified by the **sexual maturity rating** system (also known as Tanner Staging) into 5 stages (Chapter 110.1). Maturation can sometimes occur asymmetrically owing to fluctuation of the hormonal environments and various end organ sensitivities. Lack of development by age 13 yr is considered delayed and warrants endocrinology evaluation. Menarche usually occurs approximately 2 yr after initiation of breast development.

**BREAST EXAMINATION**

A breast examination should be included in the annual examination of all children and adolescents. Examination of the **newborn** includes assessment of breast size, nipple position, presence of accessory nipples, and nipple discharge. Examination of the **prepubertal girl** includes inspection and palpation of the chest wall for masses, pain, nipple discharge, and signs of premature thelarche. Examination of the **adolescent** is performed with the patient in the supine position; the arm ipsilateral to the breast that is being examined should be placed next to the patient’s head. The breast tissue is examined with the flat pads of the middle fingers, and the examiner can feel for abnormalities on the breast with a pattern similar to spokes on a wheel, in a circular clockwise pattern with concentric circles or by moving in a rotary fashion around the breast. Whatever the method used, the goal is to palpate all the breast tissue in a uniform fashion. The sexual maturity rating should be noted and axillary, supraclavicular, and infraclavicular nodes evaluated for lymphadenopathy. The areola should be compressed to assess for nipple discharge.

**BREAST SELF-EXAMINATION**

Controversy exists as to the utility of breast self-examination in the adolescent population. Experts believe that it might be ill advised to encourage breast self-examination in the adolescent because of a potential for unnecessary anxiety and possible unwarranted treatment in a population that is at low risk for malignant disease. The American College of Obstetricians and Gynecologists states that despite a lack of definitive data for or against breast self-examination, breast self-examination may be recommended beginning at age 19 yr. Women with previous exposure to therapeutic chest radiation therapy are advised to begin breast self-examination 8 yr after radiation therapy.

**ABNORMAL DEVELOPMENT**

**Neonatal Breast Abnormalities**

The condition in which breasts enlarge in the newborn period is neonatal breast hypertrophy. This is quite common in term infants of either sex and can occur as a result of elevated circulating maternal endogenous steroid hormones in late gestation. As maternal estrogen levels fall, prolactin levels can increase and the breasts can produce a clear or cloudy (milk-like) nipple discharge (“witch’s milk”) in male and female infants. Repeated manipulation of the breast can exacerbate the condition. On occasion, the hypertrophy is associated with mastitis caused by a staphylococcal or streptococcal infection; antibiotics should be administered.

**Precocious Puberty**

Premature thelarche is usually an isolated condition and is more common than previously thought. In one study, patients with a sexual maturity rating 2 or greater at 7 yr of age were 10.4% of white, 23.4% of black non-Hispanic, and 14.9% of Hispanic girls. However, it may also be the first symptom of precocious puberty. Precocious puberty occurs in 14-18% of girls with premature thelarche (see Chapter 562). Serial examinations, with particular emphasis on growth velocity, secondary sex characters such as pubic hair, pigmentation of the labia or areola, or vaginal bleeding are imperative to identify precocious puberty. Unless there are associated signs of precocious puberty, the parents should be reassured and the child should be followed.

**Amastia**

Complete absence of the breast, or amastia, is rare and is thought to occur from lack of formation or obliteration of the mammary ridge. Amastia is usually unilateral and can be congenital or associated with systemic disorders (e.g., ectodermal dysplasia, Crohn disease) or endocrine disorders (e.g., congenital adrenal hyperplasia, gonadal dysgenesis, hypogonadotrophic hypogonadism). Novel gene mutations have been discovered that may be linked to syndromic amastia, including PTTRF, a protein tyrosine receptor type F gene, and ectodysplasin A receptor (EDAR). It can be associated with anomalies of the underlying mesoderm, such as abnormal pectoralis muscles seen in Poland syndrome (aplasia of the pectoralis muscles, rib deformities, webbed fingers, and radial nerve aplasia) (Fig. 551-1). Amastia or hypomastia can also be iatrogenic, resulting from injuries sustained during thoracotomy, chest tube placement, radiotherapy, severe burns, and inappropriate biopsy of the breast bud. Treatment is surgical correction.

**Polymastia and Polythelia**

Supernumerary breast tissue (polymastia) and accessory nipples (polythelia) occur in approximately 1-6% of the population (Fig. 551-2). The abnormally placed tissue can be seen anywhere along the mammary ridges as a result of incomplete involution but is usually noted on the chest, upper abdomen, or just inferior to the normally positioned breast. There is an association between polythelia and anomalies of the urinary and cardiovascular system. Surgical excision of the accessory breasts or nipple is not usually needed. Resection of accessory tissue may be warranted if the patient has pain or for cosmetic reasons.

**Breast Asymmetry and Hypomastia**

Some degree of asymmetry is normal in women, and it may be more pronounced during puberty while the breasts are developing.

**Figure 551-1** Preoperative frontal view of a patient with left breast hypoplasia secondary to Poland syndrome. (From Sadove AM, van Aalst JA: Congenital and acquired pediatric breast anomalies: a review of 20 years’ experience, Plast Reconstr Surg 115:1039–1050, 2005, Fig. 12A.)
Hypoplasia of the breasts varies in degree from a nearly total absence of breast tissue to well-formed breasts that are considered by the patient to be too small. There are several causes for poor or absent breast development. The onset of breast development may be delayed in all other respects; a patient's family history might include late breast development. Other causes include ovarian dysfunction, hypothyroidism, and chest wall irradiation or surgery. Hypoplastic breast tissue can also be associated with a tuberous breast anomaly.

Surgical correction is an option for women with marked asymmetry and with no other associated pathology should be reassured. Surgical intervention often necessitates relocation of the nipple, which can result in decreased sensation and altered lactation, and it is not uncommon for the lesion to recur.

### INFECTIONS
Mastitis is the most common infection of the breast. Although it is most common in lactating mothers, it can occur in young infants and adolescents. Neonatal mastitis is an infection that usually occurs in term or near-term infants. It should be treated aggressively to reduce the risk of forming abscesses. Adolescents can develop nonlactational mastitis or a breast abscess for unknown reasons, as a result of irritation of the skin (through shaving or nipple stimulation), trauma, a foreign body (e.g., piercing), ductal abnormality (such as ductal ectasia), or infection of an epidermal cyst. The initial therapy of all breast infections is antibiotics and analgesics. *Staphylococcus aureus* (see Chapter 181.1) or anaerobic bacilli (*bacteroides*) are the offending organism is almost all cases, and methicillin-resistant *S. aureus* coverage should be considered in communities where prevalence is high. Owing to the potential for breast abscess, the neonatal population should be treated with parenteral antibiotics for methicillin-resistant *S. aureus* or guided by gram stain, when available. Adolescents may be initially treated with warm compresses and oral antibiotics. Abscesses should be surgically evaluated (with ultrasound guidance if necessary) and drained as necessary. If incision and drainage is performed, a small, periareolar incision is indicated.

### TRAUMA AND INFLAMMATION
Breast trauma is common in adolescent girls participating in contact sports. The trauma usually takes the form of contusion or hematoma and can resolve spontaneously or may be associated with late cystic changes in the breast or fibrosis with retraction of the skin or the nipple over the injured area.

### NIPPLE DISCHARGE
Nipple discharge must be carefully evaluated and a distinction made among galactorrhea (milky white discharge), blood, or other discharge (Table 551-2). A careful history and physical examination directed at the possible etiologies of galactorrhea will help the practitioner determine the etiology. Examination of the discharge assists in diagnosis. Benign conditions are usually associated with a milky, sticky, thick discharge; infection is associated with a purulent discharge; intraductal papilloma and cancer are associated with a serous, serosanguineous, or bloody discharge. Preoperative evaluations by mammography, hemocult, ductography, and cytology are poor predictors of histologic diagnosis. Therefore, patients with pathologic nipple discharge should undergo biopsy for accurate diagnosis.

### Galactorrhea
Cytologic evaluation of nipple discharge is not recommended. Serum pregnancy testing and prolactin and thyroid levels are obtained to rule out the presence of a thyroid abnormality, a pituitary prolactinoma, and pregnancy (in the postpubertal adolescent). If the prolactin level

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**Table 551-1** Differential Diagnosis of Macromastia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile hypertrophy</td>
<td>Adrenal cortical tumors</td>
</tr>
<tr>
<td>Tumors of the breast</td>
<td>Exogenous hormones</td>
</tr>
<tr>
<td>Giant fibroadenoma</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Cystosarcoma phyllodes</td>
<td>Gonadotropins</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Corticosterone</td>
</tr>
<tr>
<td>Hormonally active tumors</td>
<td>Medications</td>
</tr>
<tr>
<td>Ovarian granulosa cell tumor</td>
<td>Cannabis</td>
</tr>
<tr>
<td>Ovarian follicular cysts</td>
<td></td>
</tr>
</tbody>
</table>

is elevated, visual field studies and a head MRI might reveal presence of a pituitary adenoma (see Chapter 560). Treatment is directed by results of history, physical exam, and lab studies. Patients should be instructed to avoid nipple stimulation and stop any offending drugs. Hypothyroidism should be treated and prolactin tumors managed with appropriate medical or surgical care. Treatment of galactorrhea (not thyroid related) consists primarily of dopamine agonists such as bromocriptine or cabergoline. Surgical intervention, usually transphenoidal hypophysectomy, is rarely required.

**Bloody Discharge**

In adolescent athletes, bloody discharge may be due to chronic nipple irritation (jogger’s nipple), discharge from the ducts of Montgomery (on the edge of the areola, not through the nipple) or duct ectasia. Cytologic assessment should be performed. Surgical consultation for a mass is indicated because intraductal breast papillomas have occurred in adolescents. However, there have been no reported cases of breast cancer in infants. Bloody nipple discharge in infants is most likely from mammary duct ectasia, and if the following studies are positive (prolactin, estradiol, thyrotopin, and ultrasound) then watchful waiting may be appropriate.

**Mastalgia**

The most common causes of breast pain in adolescents are exercise and benign breast changes. Physiologic swelling and tenderness occur on a cyclic basis, most commonly during the premenstrual phase, and are secondary to hormonal stimulation and resulting proliferative changes. Hormonal imbalance can cause exaggerated responses in the breast tissue, especially in the upper and outer quadrants. Nodularity, poorly localized tenderness, and a soreness radiating to the axilla and arm are usual accompanying findings. The preferable term for these changes is benign breast changes rather than fibrocystic disease. Treatments recommended for this condition and exercise-induced pain include a firm supportive sports-type bra, heat, and analogics. Oral contraceptives often improve the breast pain. A course of nonsteroidal antiinflammatory drugs is also effective. Methylxanthines (caffeine in coffee, tea, carbonated drinks) and smoking should be eliminated. Evening primrose oil and vitamin E are popular but unproven treatments.

**Breast Masses in the Adolescent Girl**

**Table 551-2: Common Causes of Nipple Discharge**

- Pregnancy
- Medicines
- Hormones (oral contraceptives, estrogen, progesterone)
- Blood pressure drugs (methylodopa, verapamil)
- Tricyclic antidepressants
- Tranquilizers (antipsychotics)
- Antinausea drugs (metoclopramide)
- Herbs (nettle, fennel, blessed thistle, anise, fenugreek seed)
- Illicit drugs (marijuana, opiates)
- Stimulation of the breast (sexual or from exercise)
- Thyroid abnormalities
- Chronic emotional stress
- Hypothalamic tumors
- Chest wall conditions
- Herpes zoster
- Trauma
- Burns
- Tumors
- Breast conditions
- Mammary duct ectasia
- Chronic cystic mastitis
- Intraductal cysts
- Intraductal papillomas

**Table 551-3: Breast Masses in the Adolescent Girl**

**BENIGN**
- Fibroadenoma
- Fibrocystic changes or cysts
- Unilateral thelarche
- Hemangioma
- Intraductal papilloma
- Fat necrosis
- Abscess
- Mastitis
- Lipoma
- Hematoma
- Hamartoma
- Macromastia (juvenile hypertrophy)
- Galactocele
- Intraductal papilloma
- Juvenile papillomatosis
- Lymphangiomia

**MALIGNANT**
- Malignant cystosarcoma phyllodes
- Breast carcinoma
- Metastatic disease
- Lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia


The most common solid mass seen in adolescent girls is the fibroadenoma. Fibroadenomas are most often located in the upper outer quadrant of the breast. The average size is 2-3 cm, and 10-25% of patients have multiple lesions. The physical examination is usually diagnostic because these lesions are well circumscribed, rubbery, mobile, and not tender. In equivocal cases, an ultrasound may be helpful in making the diagnosis. Mammography is not indicated in the adolescent patient.

Fibroadenomas can develop because of a local exaggerated response to estrogen stimulation, and they can enlarge during the menstrual cycle. These lesions may be safely watched for at least 2 menstrual cycles, and some investigators suggest observation until adulthood. Approximately 10% of fibroadenomas regress spontaneously. The option of expectantly managing the patient until adulthood should be considered because the risk of primary cancer is very low in this population. If expectant management is chosen, serial ultrasounds every 6-12 mo may be done to ensure that the mass does not have malignant characteristics on imaging and that it is not enlarging or changing in contour until it starts regressing at which time the ultrasounds can be done on longer intervals. Approximately 4% of fibroadenomas grow, and so fine-needle aspiration or excision is recommended when a mass is enlarging, grows >5 cm (because of the risk of giant fibroadenoma or cystosarcoma phyllodes), or the mass is causing anxiety to the thorlarche should be recognized to avoid biopsy and potential injury to the maturing breast. If there is any question, ultrasound can be used to evaluate for a mass. Unilateral thelarche has also been reported as a side effect of cimetidine and is reversible when the medication is stopped.

**Common Adolescent Breast Masses**

**Table 551-3** shows the differential diagnosis for breast masses in the adolescent patient. The patient should be questioned about the variation in symptoms with the menstrual cycle, associated symptoms such as nipple discharge, recent trauma to the breast, family history of breast masses or cancer, and history of chest radiation or malignancy. Because breast cancer in the adolescent is extremely rare, masses can be expectantly managed for extended periods with little concern for malignancy in this population.

The most common solid mass seen in adolescent girls is the fibroadenoma. Fibroadenomas are most often located in the upper outer quadrant of the breast. The average size is 2-3 cm, and 10-25% of patients have multiple lesions. The physical examination is usually diagnostic because these lesions are well circumscribed, rubbery, mobile, and not tender. In equivocal cases, an ultrasound may be helpful in making the diagnosis. Mammography is not indicated in the adolescent patient.
patient or her family. Combined estrogen-progesterone birth control pills have been found to be protective of fibroadenomas.

Cysts are very common masses seen in the pediatric breast. Cysts vary in size over the course of a menstrual cycle, so a patient with a possible cyst should be reexamined a few weeks after the initial evaluation to see if the mass is still present. If a mass persists, then it may be imaged by sonography or aspirated with a needle to evaluate if it truly is a cyst. Aspirated fluid that is clear may be discarded. Bloody fluid and other aspirated material should be sent for cytology. Cystic lesions that resolve with aspiration should be reevaluated in 3 mo. If they recur they should be evaluated with sonography.

Malignant Masses
Primary breast cancer is extremely rare in adolescents. Surveillance Epidemiology and End Results data from 1975-2009 establishes an incidence of invasive breast cancer of 0.2/100,000 for females ages 15-19 yr and 1.6/100,000 for females ages 20-24 yr. Although malignancy is rare, lesions with suspicious imaging findings or progressive growth should undergo cytologic or histologic examination. A small study in Austria noted a 4.7% malignancy rate among palpable masses in teens.

Cystosarcoma phyllodes can occur in adolescents and has been reported in a child as young as 10 yr old. It is characterized by asymmetric breast enlargement in association with a firm, mobile, circumscribed mass. It can mimic a giant fibroadenoma. The tumor often grows rapidly and can become quite large. The majority of these tumors have a favorable prognosis, but malignant cystosarcoma phyllodes has been reported to recur both locally and with metastases. Fatal metastatic cystosarcoma phyllodes in an adolescent has occurred. Excision with 1 cm margins is the preferred initial therapy in adolescent patients, regardless of the histologic classification of the lesion.

Juvenile papillomatosis is a marker for increased breast cancer risk in family members, and in patients with these, up to 15% may have a juvenile secretory carcinoma. Treatment of juvenile papillomatosis is total resection of the lesion with preservation of the breast.

Secondary cancers in adolescents with previous therapeutic radiation to the chest or with malignancies with the potential to metastasize to the breast should be monitored more closely for breast masses. Rhabdomyosarcoma is the most common to metastasize to the breast. Breast tumors also may be the first manifestation of relapse (extramullary) in acute lymphoblastic leukemia.

Imaging of Breast Masses
Because the dense breast tissue of the adolescent obstructs the visualization of a palpable mass, mammography is not advised for this age group. Ultrasonography is the imaging modality of choice for breast abnormalities in the pediatric population. Color Doppler ultrasound can be useful in evaluating breast abnormalities such as fibroadenomas or abscesses.

Recommendations for Daughters of Women with Breast Cancer
Risk Reduction
There are a limited number of things that young women can do to lower their risk of breast cancer. The American Cancer Society recommends regular physical activity, limiting alcohol, and maintaining a healthy weight. Breastfeeding has a slight effect on breast cancer risk and that effect is only among women who have breastfed for a long time. Breastfeeding seems to be more protective against the most aggressive types of breast cancer, including tumors in women with mutations in the BRCA-1 gene, hormone-receptor negative, and possibly triple-negative tumors.

Screening Procedures
Breast self-examination is an option for women starting in their 20s. Women should be told about the benefits and limitations of breast self-examination. Women should report any breast changes to their health professional. Women in their 20s and 30s should have a clinical breast exam as part of a periodic (regular) health exam by a health professional, at least every 3 yr. After age 40 yr, women should have a breast exam by a health professional every year and a screening mammogram every year and should continue to do so for as long as they are in good health.

Genetic Testing in Children
Genetic testing for mutations in cancer susceptibility genes in children is particularly complex. Both parents and providers may request or recommend testing for minor children; however, many experts (including the American Society of Clinical Oncology) recommend that unless there is evidence that the test result will influence the medical management of the child or adolescent, genetic testing should be deferred until legal adulthood (18 yr or older) because of concerns about autonomy, potential discrimination, and possible psychosocial effects.

COSMETIC SURGERY
A dramatic increase in adolescents desiring breast augmentation has occurred since the turn of the century. Breast augmentation in adolescents is discouraged owing to associated psychologic and physical immaturity. The American Society of Plastic Surgeons discourages breast augmentation in girls younger than age 18 yr for purely cosmetic reasons. The FDA also considers breast implants in adolescents younger than age 18 yr for solely cosmetic reasons to be an off-label use.

Breast reduction surgery might be considered when an adolescent is bothered by extremely large breasts that result in neck and back pain and prevent participation in sports. Breast reduction allows these girls to feel less self-conscious, have less pain, and be more active. Also girls with marked asymmetry in breasts from the pathologies noted earlier can feel self-conscious and request breast surgery. Before performing breast-altering surgery, practitioners must ensure proper selection of teens and families who have an appropriate understanding of the risks and benefits of surgery and realistic expectations of the procedure.

Bibliography is available at Expert Consult.
Breast Concerns

**Bibliography**


POLYCYSTIC OVARY SYNDROME

Etiology and Definition

Polycystic ovary syndrome (PCOS) is a common disorder of reproductive hormone function that is characterized by the triad of oligoovulation or anovulation, clinical or biochemical hyperandrogenism, and ovaries with a polycystic morphology on ultrasound examination (≥12 follicles in 1 ovary and/or ovarian volume >10 mm³). Various expert bodies prioritize these elements differently for establishing the diagnosis, and few require the presence of all 3 (Table 552-1). Hyperandrogenism with ovulatory dysfunction (with exclusion of other causes) is most often considered sufficient for diagnosis in the United States. Abnormalities commonly associated with PCOS include obesity, insulin resistance, and the metabolic syndrome, but the phenotype is variable and affected individuals may display none of these. The disorder, affecting 5-8% of women of reproductive age, typically emerges in adolescence when a normal menstrual pattern is not established and there is clinical evidence of androgen excess.
**Pathology Pathogenesis and Genetics**

PCOS has a high concordance rate in twins, and in some studies either epigenetic or dominant inheritance patterns are observed. Nonetheless, a consistent hereditary pattern has not been identified.

Gonadotropic dysregulation with increased luteinizing hormone (LH) pulsatility and abnormally high ratios of circulating LH to follicle-stimulating hormone (FSH) are found in many patients with PCOS. Increased ovarian production of androgen in response to LH and impaired folliculogenesis owing to lower FSH are attributed to this gonadotropic pattern. Abnormal regulation of gonadotropin-releasing hormone agonist and abnormal gonadotropin secretion more likely reflect the abnormal hormonal milieu of the syndrome than explain its origin (Fig. 552-1). An increased ratio of circulating levels of LH:FSH is not a diagnostic criterion for PCOS.

Alterations in activities of steroidogenic enzymes that would explain ovarian androgen hyperfunction are seen in PCOS subjects, but they are not consistently present in all patients and it is unclear whether these alterations are a cause of PCOS or are a consequence of ovarian dysregulation. The mass of ovarian stromal cells responsible for androgen production is increased, and surgery that reduces this ovarian component (ovarian wedge resection, or laparoscopic ablative procedures) reduces circulating androgen levels and often restores ovarian cyclicity. Patients with hyperandrogenic congenital or adult-onset adrenal hyperplasia exhibit PCOS-like ovarian dysfunction that can be reversed by reducing the adrenal-derived androgens with glucocorticoid therapy. A primary role for androgen excess in the pathophysiology of all instances of PCOS seems unlikely; many patients have minimal hyperandrogenism, and elimination of androgen excess (with gonadotropin-releasing hormone agonists) does not affect associated insulin resistance.

Measures of insulin resistance are greater and more prevalent among women with PCOS than controls even when accounting for body mass index (BMI). Insulin enhances ovarian androgen production directly and contributes to elevations of free testosterone levels through its suppression of hepatic production of sex steroid-binding globulin. Treatment with insulin sensitivity-enhancing agents that can reduce insulin levels is associated with modest reductions in measures of androgen excess and, in some patients, restoration of regular ovulation. The association of insulin resistance with weight might explain the appearance of features of PCOS among some women who gain weight as well as the resolution of PCOS among affected women who lose weight.

**Clinical Manifestations**

PCOS, a lifelong disorder, commonly becomes manifest as puberty progresses, but its onset can occur later during young adulthood.

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**Table 552-1** Diagnostic Criteria for Polycystic Ovary Syndrome

<table>
<thead>
<tr>
<th>NATIONAL INSTITUTES OF HEALTH CRITERIA</th>
<th>ROTTERDAM CRITERIA</th>
<th>ANDROGEN EXCESS SOCIETY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligo or anovulation and Clinical or biochemical hyperandrogenism</td>
<td>Two of 3 of the following: Oligo or anovulation Polycystic ovaries on ultrasonography (12 or more follicles in a single ovary or ovarian volume of &gt;10 mm³ in 1 ovary) Clinical and/or biochemical hyperandrogenism</td>
<td>Clinical or biochemical hyperandrogenism and at least 1 of the following: Polycystic ovaries or Oligo or anovulation</td>
</tr>
</tbody>
</table>

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**Figure 552-1** Schematic of pathophysiology of polycystic ovary syndrome and mechanism of therapeutic drugs. DHT, dihydrotestosterone; LH, luteinizing hormone; OCPs, oral contraceptive pills; SHBG, sex hormone-binding globulin. (Adapted from Hassan A, Gordon CM: Polycystic ovary syndrome in adolescence, Curr Opin Pediatr 19[4]:389–397, 2007.)
Clinical hallmarks are menstrual abnormalities and manifestations of hyperandrogenism but the severity of the disorder is variable (Table 552-2). Ovulation is typically irregular or absent, and menses are consequently irregular or absent. When menstrual bleeding does occur, it may be anovulatory bleeding, which is often heavy and/or protracted as a result of an extended period of unopposed endometrial growth. Alternatively, bleeding can be relatively normal in character as a consequence of a preceding ovulation. Protracted spells of anovulation, with accompanying unopposed estrogen is a risk factor for endometrial hyperplasia, and more severe premenopausal and frankly malignant changes may eventuate.

The diagnosis of PCOS in adolescents may be made on the basis of a lack of resolution of the normal pattern of anovulatory menstrual cycles present in the 1st 2 postmenarchial years. Less commonly, the diagnosis is made in the setting of primary amenorrhea. Serum androgen levels may be elevated and clinical findings of androgen excess are common, although distinction of normal androgenic expressions of puberty (acne, mild hirsutism) from early manifestations of PCOS may be difficult and serum hormonal testing may be helpful.

Obesity is common among affected women, and in some patients expression of PCOS features is conditional on elevation of BMI and reversible with weight loss. However, there is a subset of patients present with a “lean” PCOS phenotype and thus absence of excess weight should not preclude consideration of the PCOS diagnosis. PCOS is associated with an increased prevalence of insulin resistance and type 2 diabetes independent of the tendency for many affected patients to have an elevated BMI. Additionally, PCOS confers a substantial and specific increase in risk for metabolic syndrome (hyperlipidemia, insulin resistance, type 2 diabetes) in adolescent girls after accounting for BMI.

**Laboratory Findings, Diagnosis, and Differential Diagnosis**

The diagnosis of PCOS requires exclusion of disorders that would otherwise account for hyperandrogenism and anovulation. Serum 17-hydroxyprogesterone should be measured when there is clear androgen excess to screen for adult-onset 21-hydroxylase deficiency (see Chapter 576). In the adolescent with amenorrhea but minimal hyperandrogenic findings, consideration should be given to functional hypothalamic suppression as a result of excessive exercise and/or dieting, and a careful history taken to rule out such behavioral patterns. All patients should be clinically evaluated for Cushing syndrome, and biochemical evaluation is indicated when findings, including hypertension and/or characteristic body habitus features, are suggestive (see Chapter 577). The 2 disorders have in common a tendency for overweight and varying degrees of insulin resistance and androgen excess, but they differ in that Cushing syndrome demonstrates muscle wasting as a result of catabolism.

Evidence for androgen excess that is rapid in onset and/or severe especially if masculinizing, warrants measurement of androgens (total testosterone, dehydroepiandrosterone [DHEAS]) to exclude the possibility of an androgen-secreting adrenal or ovarian tumor. The laboratory evaluation is completed with the exclusion of hyperprolactinemia, premature ovarian failure, and thyroid disease as causes of anovulation: determinations of functional hyperprolactinemia, FSH, and thyroid-stimulating hormone, respectively.

The diagnosis of PCOS is confirmed from the constellation of oligoovulation or anovulation, androgen excess (clinically or with biochemical confirmation), and typical ovarian morphology on ultrasound. Various experts weigh these 3 features differently and do not, as a rule, require the presence of all (see Table 552-1). Young women often exhibit the ovarian appearance of PCOS without any other evidence, and not all patients with PCOS by the criteria of hyperandrogenism and ovulatory disruption exhibit ovarian changes typical of PCOS. Ultrasound study to diagnose PCOS is not always required if oligoovulation and features of androgen excess are present. Clinical androgen excess (particularly acne) often appears in late puberty and does not necessarily signal PCOS. Nevertheless, young women with persistent oligoovulation or anovulation, accompanied by androgen excess, will likely have persistence of these symptoms and should be considered to have PCOS.

Insulin resistance is common among women with PCOS, and although not requisite for diagnosis, should be considered when PCOS is likely. Adolescents with hyperandrogenemia and anovulation should be evaluated for diabetes or impaired glucose tolerance with a 2 hr (75 g glucose load) glucose tolerance test.

**Complications and Long-Term Outlook**

Fertility management, prevention of endometrial cancer, and reduction in the likelihood and severity of the common accompanying metabolic disorders are long-term tasks for the PCOS patient and her healthcare providers (Table 552-3). Notwithstanding its reversibility with weight loss in some patients and a tendency to ameliorate in some women later in reproductive life, PCOS usually requires management throughout the reproductive years. Young patients should be counseled that modern fertility management allows most affected women to have children without great difficulty, and they should also know that the disorder does not confer reliable protection from unintended pregnancy. Endometrial cancer can develop as early as the 3rd decade in women with PCOS who are not managed with progestins or ovulation induction; patients should understand the importance of long-term strategies for endometrial protection. Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome are more common among obese adolescents with PCOS; their prevalence increases over time. Weight control through diet and lifestyle measures, detection and management of impaired glucose tolerance and diabetes, and management of abnormal lipids are targets for long-term management.

**Treatment**

Management focuses on the menstrual abnormalities, symptoms of androgen excess, and associated metabolic changes. Weight loss through lifestyle change, use of hormonal contraceptive agents for menstrual regulation as well as androgen suppression, antiandrogens as adjuncts for hirsutism treatment, and insulin-sensitizing agents are common components of treatment.

### Table 552-2: Phenotypes for Polycystic Ovary Syndrome Based on 2003 Rotterdam Criteria

<table>
<thead>
<tr>
<th>SIGNS, RISKS, AND PREVALENCE</th>
<th>SEVERE PCOS</th>
<th>HYPERANDROGENISM AND CHRONIC ANOVULATION</th>
<th>OVULATORY PCOS</th>
<th>MILD PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periods</td>
<td>Irregular</td>
<td>Irregular</td>
<td>Normal</td>
<td>Irregular</td>
</tr>
<tr>
<td>Ovaries on ultrasonography</td>
<td>Polycystic</td>
<td>Normal</td>
<td>Polycystic</td>
<td>Polycystic</td>
</tr>
<tr>
<td>Androgen concentrations</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Milder raised</td>
</tr>
<tr>
<td>Insulin concentrations</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Risks</td>
<td>Potential long-term</td>
<td>Potential long-term</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Prevalence in affected women</td>
<td>61%</td>
<td>7%</td>
<td>16%</td>
<td>16%</td>
</tr>
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</table>

PCOS, polycystic ovary syndrome.

**Table 552-3** Lifelong Health Complications

<table>
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<tr>
<th>PREGNATAL OR CHILDHOOD</th>
<th>ADOLESCENCE, REPRODUCTIVE YEARS</th>
<th>POSTMENOPAUSAL</th>
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<tr>
<td>REPRODUCTIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature adrenarche</td>
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<tr>
<td>Early menarche</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Menstrual irregularity</td>
<td>Delayed menopause?</td>
</tr>
<tr>
<td></td>
<td>Hirsutism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td></td>
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<tr>
<td></td>
<td>Infertility</td>
<td></td>
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<tr>
<td></td>
<td>Endometrial cancer</td>
<td></td>
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<td></td>
<td>Miscarriage</td>
<td></td>
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<tr>
<td></td>
<td>Pregnancy complications</td>
<td></td>
</tr>
<tr>
<td>METABOLIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal fetal growth</td>
<td>Obesity</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>Impaired glucose tolerance</td>
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<tr>
<td></td>
<td>Insulin resistance</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>OTHER</td>
<td>Sleep apnea</td>
<td>Cardiovascular disease?</td>
</tr>
<tr>
<td></td>
<td>Fatty liver</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
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</tbody>
</table>


**Lifestyle Changes**

Several studies have shown that comprehensive lifestyle programs for overweight and obese women with PCOS aimed at fitness and weight loss can yield high rates of restoration of normal menstrual function, reduction of free androgen index, reduction in measures of insulin resistance, and improvements in serum lipids. Limited data show similar benefits from such interventions for obese adolescents with PCOS. Successful weight loss programs for adolescents with PCOS using both psychologic and nutritional counseling do result in improved menstrual function.

**Hormonal Contraceptives**

Combined (estrogen and progestin) hormonal contraceptive medications are considered first-line therapy for adults not desiring fertility and for adolescents (see Chapter 117). Adolescents with PCOS are at risk for unintended pregnancy; their fertility would be expected to be reduced relative to that of their peers, but they are still at risk for pregnancy.

Avoidance of hyperplastic endometrial states resulting from unopposed estrogen and management of abnormal uterine bleeding in anovulatory episodes can be accomplished with the use of combined hormonal contraceptives. The progestational component inhibits endometrial proliferation and the schedule of pill administration predictably regulates menstrual bleeding. The estrogenic component of combined oral contraceptive elevates circulating sex hormone-binding globulin, which reduces free and bioavailable testosterone levels. Both of the hormonal elements in oral contraceptives combine to suppress gonadotropin (particularly LH) stimulation of ovarian androgen production. DHEAS levels, often contributory to hyperandrogenemia in PCOS, are usually decreased by combined contraceptive use. Products with less-androgenic progestational components (drospirenone, desogestrel) may provide better relief from androgenic symptoms.

Using a product that is well tolerated in long-term use is more important than using a product with particular progestational component. Products with reduced frequency and duration of pill-free intervals can provide superior androgen suppression and a welcome decrease in frequency of bleeding episodes. Depot medroxyprogesterone acetate for contraception, endometrial protection, and androgen suppression may be a suitable alternative to combined hormonal contraceptives; it provides even more profound suppression of ovarian androgen production, but it does not elevate sex hormone-binding globulin. Low-dose progestin-only regimens (oral minipills, implantable progestational contraceptives, and progestin-releasing intratubal devices) also provide effective endometrial protection but would be expected to provide only partial and/or inconsistent androgen suppression, would not elevate sex hormone-binding globulin, and have not been shown to be consistently helpful in regard to abnormal bleeding patterns.

Patients without the need for management of hyperandrogenic symptoms or contraception are often treated with periodic use of oral progestins to induce predictable menstrual bleeding and prevent endometrial hyperplasia and malignancy. Twelve-day courses of medroxyprogesterone acetate 10 mg daily or norethindrone acetate 5 mg daily are effective and safe for this purpose when taken every 1-2 mo.

**Metformin**

Metformin is a biguanide medication used to treat type 2 diabetes, its only FDA-approved indication. It has been used in a variety of settings and with differing objectives for patients with PCOS. Metformin exerts its principal effect by reducing hepatic production of glucose and limiting intestinal absorption of glucose. Studies show that a subset of women with PCOS resume regular ovulation and menses when treated with metformin, obviating the need for progestational therapy or ovulation-induction medications to protect endometrial health. For some patients the resulting normal reproductive function is appealing regardless of interest in fertility.

Metformin reduces insulin resistance and the levels of androgens. Its extended use can reduce the likelihood of development of impaired glucose tolerance or the progression of impaired glucose tolerance to type 2 diabetes; these effects are not yet proved for patients with PCOS. It should not be used in the presence of renal or hepatic impairment.

Typical dosing is 1,500-2,000 mg/day, achieved through gradual increments because gastrointestinal intolerance is common. Long-acting preparations are helpful when gastrointestinal intolerance is a problem.

The use of metformin in the treatment of PCOS depends on the patient’s goals and preference. For the treatment of hyperandrogenic symptoms, metformin effects may be modest compared to other available agents. There are no empiric data supporting the theoretical benefits of long-term use of metformin in adolescents with PCOS and obesity compared to the outcomes achieved with weight loss and oral contraceptive medications. Use of metformin as a first-line agent is favored by some experts, in part for improvement in serum measures of intermediate outcomes, and in part because of evidence in other populations of reduced progression of insulin resistance. There is no evidence for long-term benefit to clinical outcomes of adding metformin to treatment for women managed primarily with oral contraceptives. For adolescents receiving metformin as a first-line medication, progestational management (combined contraceptives or periodic progestins) will still be necessary for those not resuming ovulatory function and oral contraceptives may still be an important adjunct for management of clinical hyperandrogenism and/or contraception.

**Antiandrogens**

Antiandrogenic medications may be added to other therapies or used alone for the treatment of hirsutism. These agents are usually used integrally or adjunctively with ovarian hormonal suppression, in part because of better reduction in hirsutism when antiandrogens are combined with ovarian suppression but also to reduce the risk of unintended embryonic or fetal exposure. The highly active androgen antagonist and progestin, cyproterone, is available in Europe and in Canada as a single agent for treatment of hirsutism or in combination with ethinyl estradiol as an oral contraceptive with enhanced antiandrogenic profile. In the United States, spironolactone is the most commonly used antiandrogen. Spironolactone antagonizes androgens at their receptor and also impairs androgen synthesis. Doses of 100-200 mg daily are commonly used. Other agents that have been studied are finasteride, a 5α-reductase inhibitor, and flutamide, a nonsteroidal and highly specific androgen receptor antagonist. These are
rarely used because of lack of evidence of superior effectiveness, cost, and, in the case of flutamide, the potential for hepatotoxicity.

**HIRSUTISM**

Hirsutism is defined as abnormally increased terminal (mature, heavy, dark) hair growth in areas of the body where hair growth is normally androgen dependent (see Chapter 662). Its presence is a result of the combination of extent of androgenic stimulation and familial regional follicle sensitivity to androgens, which varies considerably among ethnic groups. Patients’ cosmetic concerns generally determine whether findings of hirsutism are a matter for clinical investigation and treatment. Hirsutism as an isolated finding is to be distinguished from masculinization. The latter includes alteration in muscle mass, clitoral enlargement, and voice change, generally manifesting as a rapid evolution (over months). Masculinization mandates a search for neoplastic source of androgen. Elevations of testosterone or DHEAS commonly indicate an ovarian or adrenal androgen source, respectively; specific imaging and occasionally selective catheterization studies are indicated.

Hirsutism without masculinization is common. The potential causes to consider are PCOS (when there is hyperandrogenism and anovulation), benign functional androgen excess (measurable hyperandrogenism without anovulation), idiopathic hirsutism (increased hair in androgen-dependent areas without measurable androgen excess), and adult-onset adrenal hyperplasia (Table 552-4). Patients can be primarily distinguished by evidence of ovulatory disorder by menstrual history, and for those with absent or irregular menses, a diagnosis of PCOS can be made. The remainder, for whom adult-onset adrenal hyperplasia and PCOS have been excluded, either have normal androgen levels with enhanced end-organ sensitivity owing to familial or ethnic predisposition or have a functional and benign overproduction of ovarian androgens. Measures of androgens (testosterone, DHEAS) may be normal or mildly elevated in the latter group. Testosterone suppresses circulating sex-steroid binding globulin, so states of testosterone overproduction might not be accompanied by elevated measures of total testosterone, although estimates of “free” or “bioavailable” testosterone reveal hyperandrogenism. Measures of unbound testosterone distinguish idiopathic hirsutism from mild benign hyperandrogenic states; making this distinction contributes little to patient management and adds cost. Idiopathic hirsutism (without evidence of androgen excess) usually responds to antiandrogen or androgen suppression therapy similarly to hirsutism associated with elevated androgens and anovulation (PCOS), and benign hyperandrogenism not associated with PCOS.

If hirsutism is present, and clinical evaluation excludes neoplasm, adult-onset adrenal hyperplasia, and Cushing syndrome, then management for symptoms of hyperandrogenism (regardless of whether measures of circulating androgens are elevated or not) can proceed as for patients with PCOS. Estrogen and progestin suppression of ovarian function, with or without added antiandrogen treatment, is the mainstay of therapy for these patients. Androgen suppression and/or antagonism results in gradual regression of the size and productivity of follicles in androgen-sensitive areas of the face and body, and these changes will evolve over successive and months-long generations of hair growth and shedding. Patients should therefore be advised that the effects of medical therapy accrue slowly, over many months.

*Bibliography is available at Expert Consult.*

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**Table 552-4 Causes of Hirsutism**

<table>
<thead>
<tr>
<th>PERIPHERAL</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Partial androgen insensitivity (5α-reductase deficiency)</td>
<td></td>
</tr>
<tr>
<td>HAIR-AN syndrome (hirsutism, androgenization, insulin resistance, and acanthosis nigricans)</td>
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<tr>
<td>Hyperprolactinemia</td>
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<table>
<thead>
<tr>
<th>GONADAL</th>
<th></th>
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<tbody>
<tr>
<td>Polycystic ovary syndrome (polycystic ovaries, chronic anovulation)</td>
<td></td>
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<tr>
<td>Ovarian neoplasm (Sertoli-Leydig cell, granulosa cell, thecoma, gynandroblastoma, lipid cell, luteoma, hypernephroma, Brenner tumor)</td>
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<tr>
<td>Gonadal dysgenesis (Turner mosaic with XY or H-Y antigen-positive)</td>
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</table>

<table>
<thead>
<tr>
<th>ADRENAL</th>
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<tbody>
<tr>
<td>Cushing syndrome</td>
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<tr>
<td>Adrenal hyperresponsiveness</td>
<td></td>
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<tr>
<td>Congenital adrenal hyperplasia (classic, cryptic, adult onset)</td>
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</tr>
<tr>
<td>21-Hydroxylase deficiency</td>
<td></td>
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<tr>
<td>11-Hydroxylase deficiency</td>
<td></td>
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<tr>
<td>3β-Hydroxysteroid deficiency</td>
<td></td>
</tr>
<tr>
<td>17β-Hydroxylase deficiency</td>
<td></td>
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<tr>
<td>Adrenal neoplasm (adenoma, cortical carcinoma)</td>
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</table>

<table>
<thead>
<tr>
<th>EXOGENOUS</th>
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<tbody>
<tr>
<td>Minoxidil</td>
<td></td>
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<tr>
<td>Dilantin</td>
<td></td>
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<tr>
<td>Cyclosporine</td>
<td></td>
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<tr>
<td>Anabolic steroids</td>
<td></td>
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<tr>
<td>Acetazolamide (Diamox)</td>
<td></td>
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<tr>
<td>Penicillamine</td>
<td></td>
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<tr>
<td>Oral contraceptives with androgenic progestins</td>
<td></td>
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<tr>
<td>Danazol</td>
<td></td>
</tr>
<tr>
<td>Androgenic steroids</td>
<td></td>
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<tr>
<td>Psoralsens</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
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<td>Phenothiazines</td>
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<table>
<thead>
<tr>
<th>CONGENITAL ANOMALIES</th>
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</tr>
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<tbody>
<tr>
<td>Trisomy 18 (Edwards syndrome)</td>
<td></td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
<td></td>
</tr>
<tr>
<td>Hurler syndrome</td>
<td></td>
</tr>
<tr>
<td>Juvenile hypothyroidism</td>
<td></td>
</tr>
</tbody>
</table>

GYNECOLOGIC MALIGNANCIES

After injuries, cancer is the second most common cause of death in adolescents. Although rare, gynecologic malignancies can be followed by infertility, depression, and poor self-image, which may be lifelong.

The most common type of gynecologic malignancy found in children and adolescents is of ovarian origin and usually manifests as an abdominal mass, which must be distinguished from other organ-based tumors and ovarian functional, physiologic, inflammatory/infectious, or pregnancy-related processes. Ovarian neoplasms constitute 1% of all childhood malignancies, but account for 60-70% of all gynecologic malignancies in this age group. Approximately 10-30% of all childhood or adolescent ovarian neoplasms are malignant. Less often, the vagina or cervix is a site of malignant lesions in children, with a few specific tumors having their greatest incidence within this population. Cervical dysplasia can occur in adolescents, and healthcare providers need to be aware of current screening guidelines as well as updates on preventive measures. Vulvar malignancies in children and adolescents are exceedingly rare.

IMPACT OF CANCER THERAPY ON FERTILITY

Chemotherapy and radiation therapy are associated with acute ovarian failure and premature menopause (Table 553-1). Risk factors include...
older age, abdominal or spinal radiation, and certain chemotherapeutic drugs, such as alkylating agents (cyclophosphamide, busulfan). Uterine irradiation is associated with infertility, spontaneous pregnancy loss, and intrauterine growth restriction. Decreased uterine volume has been noted in girls who received abdominal radiation. The vagina, bladder, ureters, urethra, and rectum can also be injured by radiation. Vaginal shortening, vaginal stenosis, urinary tract fistulas, and diarrhea are important side effects of pelvic irradiation for pelvic cancers. Pregnancy outcomes appear to be influenced by prior chemotherapy and radiation treatment; 15% of childhood cancer survivors have infertility. Cancer survivors have an increased rate of spontaneous abortions, premature deliveries, and low birthweight infants compared to their normal healthy siblings. No data support an increased incidence of congenital malformations in offspring.

Childhood cancer survivors require extensive counseling about these specific future health implications. As part of informed consent

Table 553-1 Effect of Cancer Treatment on Development of Amenorrhea

<table>
<thead>
<tr>
<th>CANCER TREATMENT PROTOCOL</th>
<th>PATIENT AND DOSE FACTORS</th>
<th>COMMON USAGE</th>
<th>FERTILITY PLANNING CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any alkylating agent (e.g., busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine) + total body irradiation</td>
<td>Conditioning for HSCT for leukemias, lymphomas, myelomas, Ewing’s sarcoma, neuroblastoma, chorioncarcinoma</td>
<td>&gt;70% of women develop amenorrhea after treatment. Any treatments containing high doses of alkylating agents and/or radiation to the abdomen, pelvis, or hypothalamic axis present the highest level of risk for gonadal impact and immediate amenorrhea. Patients should be counseled about fertility preservation before treatment.</td>
<td></td>
</tr>
<tr>
<td>Any alkylating agent + pelvic radiation</td>
<td>Sarcomas, ovarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cyclophosphamide</td>
<td>Multiple cancers: breast cancer, NHL, conditioning for HSCT</td>
<td>Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>Protocols containing procarbazine:</td>
<td>5 g/m² in women age &gt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOPP</td>
<td>7.5 g/m² in women and girls age &lt;20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEACOPP</td>
<td>&gt;3 cycles</td>
<td></td>
<td></td>
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<tr>
<td>&gt;6 cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocols containing temozolomide or BCNU + cranial radiation</td>
<td>Brain tumor</td>
<td>~30-70% of women develop amenorrhea post-treatment. Lower levels of alkylating agents and/or radiation to the abdomen, pelvis or hypothalamic axis reduce risk of immediate amenorrhea but do not eliminate risk of gonadal damage. Patients should be counseled about fertility preservation prior to treatment. For Bevacizumab, risk of amenorrhea is intermediate, yet the outcome of fertility is unknown.</td>
<td></td>
</tr>
<tr>
<td>Whole abdominal or pelvic radiation doses</td>
<td>Wilm’s tumor, neuroblastoma, sarcomas, Hodgkin lymphoma, ovarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body irradiation (TBI) doses</td>
<td>HSCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial radiation</td>
<td>Multiple cancers, breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cyclophosphamide</td>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC for breast cancer</td>
<td>Colon, non-small cell lung, head and neck, breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoclonal antibodies, e.g., bevacizumab (Avastin)</td>
<td>Colon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX,</td>
<td>Cervical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocols containing cisplatin</td>
<td>Wilm’s tumor, neuroblastoma, spinal tumors, brain tumor, relapsed ALL or NHL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal/pelvic radiation</td>
<td>Colon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-15 Gy in prepubertal girls</td>
<td>Multiple cancers, breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 Gy in postpubertal girls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lower Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocols containing nonalkylating agents or lower levels of alkylating agents (e.g., ABVD, CHOP, COP; multi-agent therapies for leukemia)</td>
<td>Hodgkin lymphoma, NHL, leukemia</td>
<td>&lt;30% of women develop amenorrhea after treatment. These treatments are unlikely to cause immediate amenorrhea at standard dosage; however, patients should be counseled that they may be at risk for early menopause. Patients may want to consider fertility preservation before or after treatment.</td>
<td></td>
</tr>
<tr>
<td>Protocols for breast cancer containing cyclophosphamide (e.g., CMF, CEF, or CAF)</td>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline + cytarabine</td>
<td>AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Very Low / No Risk</strong></td>
<td></td>
<td>Leukemia, lymphoma, breast and lung cancer</td>
<td></td>
</tr>
<tr>
<td>Multi-agent therapies using vincristine</td>
<td>Thyroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td></td>
<td>Colon, non-small cell lung, head and neck, breast</td>
<td></td>
</tr>
<tr>
<td>Monoclonal antibodies, e.g., cetuximab (Erbitux), trastuzumab (Herceptin)</td>
<td>Non-small cell lung, pancreatic, CML, GIST</td>
<td>Negligible to no effects on menses. Patients should be counseled regarding the lack of conclusive data about the reproductive effects of these drugs; fertility preservation options should be discussed.</td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors, e.g., erlotinib (Tarceva), imatinib (Gleevec)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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for cancer therapy, the possibility of infertility should be discussed with young patients and their families. Counseling and embryo or mature oocyte cryopreservation for postpubertal females before gonadotoxic therapy should be offered as standard of care. Cryopreservation of ovarian tissue for prepubertal children remains experimental and may be offered as part of a research protocol. Premature ovarian insufficiency is associated with an increased risk for cardiovascular complications, osteoporosis, and difficulties with sexual function. Risks and benefits of hormonal therapy need to be addressed.

**OVARIES**

**Neonatal and Pediatric Ovarian Cysts**

Normal follicles or physiologic ovarian cysts are seen by ultrasound examination of the ovaries in all healthy prepubertal girls. Most of these are <1 cm in diameter and not pathologic. In the neonatal period, physiologic follicular cysts as a result of maternal estrogen stimulation usually resolve spontaneously and may be followed with serial ultrasounds in the asymptomatic child. Children with an ovarian mass might have no symptoms and the mass may be detected incidentally or during a routine examination. Other children present with abdominal pain that may be accompanied by nausea, vomiting, or urinary frequency or retention. The cyst's most common complication, ovarian torsion, can result in loss of the ovary (autoamputation of the ovary has been documented to occur antenatally). Successful reports of antenatal aspiration and postnatal laparoscopic treatment exist. Large cysts (>4-5 cm), those with complex characteristics, or any ovarian cyst in premenarchal girls with associated signs or symptoms of hormonal stimulation deserve prompt evaluation. The incidence of ovarian cysts increases again with puberty.

**Functional Cysts**

Hemorrhagic cysts are an expected part of follicular development during the menstrual cycle. Normally, a dominant follicle forms and increases in size. Following ovulation, the dominant follicle becomes a corpus luteum that, if it bleeds, is termed a hemorrhagic corpus luteum. These can become symptomatic owing to size or peritoneal irritation from blood, and they have a characteristic complex appearance on ultrasound. Expectant management for a presumed functional or hemorrhagic cyst is appropriate. Physiologic cysts are usually ≤5 cm and resolve over the course of 6-8 wk during subsequent ultrasound imaging. Monophasic oral contraceptives can be used to suppress follicular development to prevent formation of additional cysts.

**Teratomas**

The most common neoplasm in adolescents is the mature cystic teratoma (dermoid cyst). Most are benign and contain mature tissue of ectodermal (skin, hair, sebaceous glands), mesodermal, or endodermal origin. Occasionally, well-formed teeth, cartilage, and bone are found. Calcification on an abdominal radiograph is often a hallmark of a benign teratoma. These tumors may be asymptomatic and found incidentally, or they can manifest as a mass or with abdominal pain (associated with torsion or rupture). If the major component of the dermoid is thyroid tissue (struma ovarii), hyperthyroidism can be the clinical presentation. Benign teratomas should be carefully resected, preserving as much normal ovarian tissue as possible. Oophorectomy (and salpingo-oophorectomy) for this benign lesion is excessive treatment. During surgery, both ovaries should be evaluated, and if there is any question about the nature of the lesion, the specimen should be evaluated by a pathologist. An association of dermoid tumors with neural elements and anti–N-methyl-D-aspartase receptor encephalitis has been reported. Excision of the ovarian tumor has led to improvement in neurologic symptoms in some patients.

**Immature teratoma** of the ovary is an uncommon tumor, accounting for <1% of ovarian teratomas. In contrast to the mature cystic teratoma, which is encountered most often during the reproductive years but occurs at all ages, the immature teratoma has a specific age incidence, occurring most commonly in the 1st 2 decades of life. By definition, an immature teratoma contains immature neural elements. Because the lesion is rarely bilateral in its ovarian involvement, the present method of therapy consists of unilateral salpingo-oophorectomy with wide sampling of peritoneal implants.

**Cystadenomas**

Serous and mucinous cystadenomas are the second most common benign ovarian tumor. These cystic lesions can become very large, yet with care, the tumor can be resected, preserving normal ovarian tissue for future reproductive potential.

**Endometriomas**

Endometriosis is a syndrome defined by the presence of ectopic endometrial tissue usually located within the pelvis and abdomen. The principal clinical symptoms in adolescents consist of severe menstrual pain and pelvic pain. Endometriomas (chocolate cysts) form when the ovaries are involved and are collections of old blood and hemosiderin within an endometrium-lined cyst. They have a typical homogeneous echogenic appearance on ultrasound and are more common in adults than in adolescents. Conservative management (suppressive therapy with ovulation suppression, and nonsteroidal antiinflammatory drugs) and ovarian cystectomy with preservation of as much functioning ovary as possible is recommended for adolescents.

**Pelvic Inflammatory Disease and Tuboovarian Abscess**

Pelvic inflammatory disease complicated by a tuboovarian abscess should be considered in a sexually active adolescent with an adnexal mass and pain on examination (see Chapter 120). These patients also typically exhibit fever with leukocytosis and cervical motion tenderness. Treatment consists of administration of intravenous antibiotics. If the lesion persists or is refractory to antibiotics, drainage of the pelvic abscess by interventional radiology should be considered.

**Adnexal Torsion**

Adnexal torsion of the ovary and/or fallopian tube can occur in children or adolescents with normal adnexa or more often those enlarged by cystic (follicular, tubal) changes or ovarian (teratoma, cystadenoma) neoplasms. When torsion occurs, the venous outflow is obstructed first, and the ovary swells and becomes hemorrhagic. Once the arterial flow is interrupted, necrosis begins. It is not known how long torsed adnexa will remain viable. When a female patient presents with acute lower abdominal pain, either episodic or constant, and if imaging studies shows unilateral enlargement of an adnexa, the diagnosis of adnexal torsion must be considered and acted upon. The sonographic presence of Doppler flow does not exclude the diagnosis of torsion. Prompt surgical intervention (laparoscopic detorsion) is warranted if clinical suspicion is high. Detorsion of the adnexa and observation for viability is recommended, with excision only for obviously nonviable necrotic tissues. Recovery of ovarian function after detorsion has been reported with identification of normal follicle development. Oophoropexy (plication) of the affected and the contralateral adnexa remains controversial.

**Ovarian Carcinoma**

Ovarian cancer is very uncommon in children; only 2% of all ovarian cancers are diagnosed in patients younger than 25 yr old. The Surveillance, Epidemiology, and End Results (SEER) incidence rates are ≤0.8/100,000 at age 0-14 yr and 1.5/100,000 at ages 15-19 yr. Germ cell tumors are the most common and originate from primordial germ cells that then develop into a number of heterogeneous tumor types including dysgerminomas, malignant teratomas, endodermal sinus tumors, embryonal carcinomas, mixed cell neoplasms, and gonadoblastomas. Immature teratomas and endodermal sinus tumors are more aggressive malignancies than dysgerminomas and occur in a significantly higher proportion of younger girls (younger than 10 yr of age). Sex-cord stromal tumors are more common among adolescents (Table 553–2). Tumor markers such as α-fetoprotein, carcinoembryonic antigen, and the antigen CA-125 are also used for diagnosis and treatment surveillance (Table 553–3).
Table 553-2  Malignant Ovarian Tumors in Children and Adolescents

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>OVERALL 5-YR SURVIVAL</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERM CELL TUMORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>85%</td>
<td>10-20% bilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most common ovarian malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gonadal dysgenesis/androgen insensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitive to chemotherapy/radiation</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>97-100%</td>
<td>All 3 germ layers present</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>80%</td>
<td>Almost always large (&gt;15 cm)</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>30%</td>
<td>Rare</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>25%</td>
<td>Can mimic ectopic pregnancy</td>
</tr>
<tr>
<td>Gonadoblastoma</td>
<td>100%</td>
<td>Endocrinologic symptoms (precocious puberty)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highly malignant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary amenorrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Virilization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45,X or 45,X/46,XY mosaicism</td>
</tr>
<tr>
<td>SEX CORD STROMAL TUMORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile granulosa stroma cell tumor</td>
<td>92%</td>
<td>Produce estrogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menstrual irregularities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isosexual precious pseudopuberty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Call-Exner bodies rare</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumor</td>
<td>70-90%</td>
<td>Virilization in 40%</td>
</tr>
<tr>
<td>Lipoid cell tumors</td>
<td>~80%</td>
<td>Produce testosterone</td>
</tr>
<tr>
<td>Gynandroblastoma</td>
<td>90% or greater</td>
<td>Rare heterogenous group with lipid-filled parenchyma</td>
</tr>
</tbody>
</table>

Table 553-3  Serum Tumor Markers

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>CA-125</th>
<th>AFP</th>
<th>hCG</th>
<th>LDH</th>
<th>E2</th>
<th>T</th>
<th>INHIBIN</th>
<th>MIS</th>
<th>VEGF</th>
<th>DHEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial tumor</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Dysgerminoma</td>
<td></td>
<td>+</td>
<td>+</td>
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<td></td>
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<td></td>
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<tr>
<td>Endodermal sinus tumor</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>Embryonal carcinoma</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mixed germ cell</td>
<td></td>
<td>+</td>
<td>+</td>
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<td></td>
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<td></td>
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<tr>
<td>Granulosa cell tumor</td>
<td>+</td>
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<td></td>
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<td></td>
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<tr>
<td>Sertoli-Leydig</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Gonadoblastoma</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Theca-fibroma</td>
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</tbody>
</table>

AFP, α-fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrosterone; E2, estradiol; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone; MIS, müllerian inhibiting substance; VEGF, vascular endothelial growth factor.

Treatment is surgical excision followed by postoperative chemotherapy that usually consists of bleomycin, etoposide, and cisplatin. Radiotherapy is sometimes administered for disease recurrence in dysgerminomas, but it is otherwise not included in routine treatment. Staging at the beginning of therapy is of the utmost importance. In rare cases, a second-look laparotomy may be indicated for neoplasms with teratomatous elements or for those incompletely resected.

Epithelial ovarian cancers account for 19% of ovarian masses in the pediatric population, with a total of 16% being malignant. These tumors manifest almost exclusively after puberty. Common presenting symptoms include dysmenorrhea, abdominal pain, abdominal distention, nausea and vomiting, and vaginal discharge. Tumors of low malignant potential are common in adolescents and account for 30% of epithelial ovarian cancers in this age group. Given the young age of this population, although not the standard of care for adult patients, consideration may be given to conserving the contralateral ovary and uterus if they appear normal. Data suggest that in patients with early-stage disease, such an approach with appropriate surgical staging results in optimal outcomes. Overall 5 yr survival rates are approximately 73%. The number of term pregnancies and use of oral contraceptives decrease the risk of invasive epithelial ovarian cancer. Young women with a family history of ovarian cancer should seriously consider using long-term oral contraceptives for the preventive benefits when pregnancy is not being sought.

**UTERUS**

Rhabdomyosarcomas are the most common type of soft-tissue sarcoma occurring in patients younger than 20 yr of age (see Chapter 500). They can develop in any organ or tissue within the body except bone, and roughly 3% originate from the uterus or vagina. Of the various histologic subtypes, embryonal rhabdomyosarcomas in the female patient most often occur in the genital tract of infants or young children. They are rapidly growing entities that can cause the tumor to be expelled through the cervix, with subsequent complications such as uterine inversion or large cervical polyps. Irregular vaginal bleeding may be another presenting clinical symptom. They are defined histologically by the presence of mesenchymal cells of skeletal muscle in various stages of differentiation intermixed with myxoid stroma.
Treatment recommendations are based on protocols coordinated by the Intergroup Rhabdomyosarcoma Study Group and consist of a multimodal approach including radiation therapy and chemotherapy. Vincristine, Adriamycin, and cyclophosphamide with or without radiation therapy are the first line of treatment. Resection rates are now very low; chemotherapy with restrictive surgery has enabled many patients to retain their uterus while achieving excellent long-term survival rates.

**Leiomyosarcomas** and **leiomyomas** are extremely rare, occurring in <2 in 10 million individuals within the pediatric/adolescent age group, although their numbers are increasing among pediatric patients with AIDS. They usually involve the spleen, lung, or gastrointestinal tract, but they could also originate from the uterine smooth muscle. Pathogenesis is thought to correlate with the Epstein-Barr virus (see Chapter 254). Despite treatment that demands complete surgical resection (and chemotherapy for the sarcomas), they tend to recur frequently.

Endometrial stromal sarcoma and endometrial adenocarcinoma of the uterine corpus are extremely rare in children and adolescents, with only case reports noted in the literature. Vaginal bleeding not associated with sexual precocity is a common presenting sign. Treatment consists of hysterectomy, with removal of the ovaries, followed by adjunctive radiotherapy and/or chemotherapy, depending on the operative findings.

**VAGINA**

**Sarcoma botryoides** is a variant of embryonal rhabdomyosarcoma that occurs most commonly in the vagina of pediatric patients. Sarcoma botryoides tends to arise in the anterior wall of the vagina and manifests as a submucosal lesion that is grape-like in appearance; if located at the cervix it could resemble a cervical polyp or polypoid mass. These lesions were formerly treated with exenterative procedures; equal success has occurred with less-radical surgery (polypectomy, conization, and local excision) and adjuvant chemotherapy with or without radiotherapy. A combination of vincristine, dactinomycin, and cyclophosphamide appears to be effective. Outcomes depend on tumor size, extent of disease at time of diagnosis, and histologic subtype. The 5-year survival rates for patients with clinical stages I-IV were 83%, 70%, 52%, and 25%, respectively.

Vaginal adenosis can lead to the development of clear cell adenocarcinoma of the vagina in females exposed to diethylstilbestrol in utero. Pregnant women at risk for miscarriage are no longer exposed to diethylstilbestrol, and thus fewer adolescent girls and young women are at risk for this unusual tumor.

A rare tumor occurring in the vagina of infants is the **endodermal sinus tumor**. This disease usually occurs in children younger than 2 yr of age, and survival rates are poor. Combination surgery and chemotherapy are appropriate. Benign papillomas can arise in the vagina of children and result in vaginal bleeding. Rarely, vaginal bleeding is secondary to leukemia or a hemangioma.

**VULVA**

Any questionable vulvar lesion should be biopsied and submitted for histologic examination. Lipoma, liposarcoma, and malignant melanoma of the vulva have been reported in young patients. The most common lesion is likely condyloma acuminata, associated with the human papilloma virus (HPV) (see Chapter 266). Diagnosis is usually made by visual inspection. Treatment consists of observation for spontaneous regression, topical trichloroacetic acid, local cryotherapy, electrocautery, excision, and laser ablation. Some products used to treat skin lesions in adults have not been approved for children, including provider application of podophyllin resin and home application of imiquimod, podoflox, and sinecatechins ointment.

**CERVIX**

Cervical cancer screening has been cytology based using the Pap test and Bethesda Classification System (Table 553-4). Advances in epidemiologic research and molecular techniques have allowed the identification of the integral role of HPV in development of cervical cancer. HPV has become an important factor in the interpretation of cytologic results and subsequent management. The discovery of HPV presents a unique target for cervical cancer prevention, with the pediatric and adolescent population at the forefront of its implementation. Two HPV vaccines (bivalent HPV2 and quadrivalent HPV4) are currently available to protect against cervical cancer, and the HPV4 vaccine also protects against genital warts and cancers of the anus, vagina, and vulva. HPV vaccines offer the best protection if all three vaccine doses are administered before the patient is ever sexually active. The American Congress of Obstetrics and Gynecology recommends vaccination for all girls and women ages 9-26 yr, and The Advi-

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**Table 553-4**  Management of Cytologic Abnormalities in Adolescents Who Are Screened in Error and Immunocompromised Women <21 Years of Age

<table>
<thead>
<tr>
<th>CYTOLOGY RESULT</th>
<th>MANAGEMENT RECOMMENDATION</th>
<th>HPV TESTING?</th>
<th>COLPOSCOPY?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>Repeat cytologic testing in 1 year</td>
<td>No</td>
<td>At 1 yr follow-up if HGSIL or greater result At 2 yr follow-up if persistent ASCUS or greater</td>
</tr>
<tr>
<td>LGSIL</td>
<td>Repeat cytologic testing in 1 year</td>
<td>No</td>
<td>At 2 yr follow-up if persistent ASCUS or greater</td>
</tr>
<tr>
<td>HGSIL</td>
<td>If colposcopy is unsatisfactory or if CIN is ungraded: excisional procedure If colposcopy is satisfactory:  • If no CIN1-3: Pap and colposcopy q6mo until 2 are negative. If persistent HGSIL without CIN1-3 identified; then excisional procedure at 2 yr  • If CIN1: (ASCUS/LGSIL protocol)  • If CIN2, CIN2-3: Pap or colposcopy q6mo until 2 are negative, or else rebiopsy at 1 yr, treat if persistent at 2 yr  • If CIN3: excisional procedure</td>
<td>No</td>
<td>Yes, immediately</td>
</tr>
<tr>
<td>ASC-H or AGC</td>
<td>There are no specific recommendations in regard to adolescents; see ASCCP guidelines for adults Endometrial biopsy is not advised in adolescents</td>
<td>No</td>
<td>Yes, immediately</td>
</tr>
</tbody>
</table>

Note: Cryotherapy and laser ablation are acceptable treatment options only for biopsy-proven CIN2+ lesion and satisfactory colposcopic examination. AGC, atypical glandular cells; ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-H, atypical squamous cell changes, high grade; ASCUS, atypical squamous cell changes of undetermined significance; CIN, cervical dysplasia; HGSIL, high-grade squamous intraepithelial dysplasia; LGSIL, low-grade squamous intraepithelial dysplasia; Pap, Papanicolaou smear.
sory Committee on Immunization Practices (http://www.cdc.gov/vaccines/schedules/hcp/index.html) recommends routine vaccination of girls ages 11-12 yr with 3 doses of quadrivalent HPV vaccine, starting as early as age 9 yr. Catch-up vaccination is indicated for girls and women ages 13-26 yr who have not been fully vaccinated. Female patients should be vaccinated even if sexually exposed; vaccination prior to exposure is ideal. Pap testing and screening for HPV DNA or HPV antibody is not required before vaccination. The American Congress of Obstetrics and Gynecology recommends that cervical cancer screening of women who have been immunized against HPV-16 and HPV-18 should not differ from that of nonimmunized women and should follow the exact same regimen.

The adolescent population presents a unique challenge to cervical cancer screening, because the prevalence of HPV is high. In adolescents ages 15-19 yr, HPV cumulative incidence rates after initiation of sexual activity are reported as 17% at 1 yr and 35.7% at 3 yr. Correlating with the natural history of an HPV infection, >90% of low-grade intraepithelial lesions regress within this age group, giving the presence of HPV in this population little clinical significance. The overall incidence of a high-grade lesion on Pap test in the adolescent population remains low (0.7%); cervical cancer is uncommon in the age group. In the United States, the Surveillance, Epidemiology, and End Results Cancer Statistics Review 1975-2006 published by the National Cancer Institute reports an incidence of invasive cervical cancer as 0.1/100,000 in 15-19 yr olds, with no cases reported before the age of 15 yr; similar rates (≤0.3 cases per 100,000 among women ages 15-19 yr) have been reported by the Canadian Cancer Registry. Therefore, colposcopy for minor cytologic abnormalities within this age group should be highly discouraged, because it will result more often in harm than produce any clinical benefit. The American Society for Colposcopy and Cervical Pathology and the American College of Obstetricians and Gynecologists guidelines recommend that adolescents should be managed conservatively and should not receive Pap smear screening until age 21 yr regardless of age of onset of sexual intercourse. If an HPV test is done, the results should be ignored. However, sexually active immunocompromised (HIV-positive patients or organ transplant recipients) adolescents should undergo screening twice within the 1st yr after diagnosis and annually thereafter. Table 553-4 demonstrates management recommendations for abnormal cytologic results for adolescents who are screened in error and immunocompromised sexually active adolescents who are screened. Routine screening for cervical cancer in the general adolescent population (younger than age 21 yr) is not recommended.

Clinic protocols that require teenagers to undergo Pap smears before prescribing contraceptives should be reconsidered in light of these recommendations.

_Bibliography is available at Expert Consult._
EMBRYOLOGY
Cellular differentiation, duct elongation, fusion, resorption, canalization, and programmed cell death are all involved in the sequence of events that occur in a developing embryo and early fetus to create a normal reproductive system. Myriad gonadal, Müllerian, and/or vulvovaginal anomalies can result from interruption of the intricate sequence or functions of any one of these processes during formation of the reproductive system (Table 554-1). Genetic, epigenetic, enzymatic, and environmental factors all have some role in the process (Table 554-2).

Phenotypic sexual differentiation, especially during formation of the vulvovaginal and Müllerian systems, is determined from genetic (46,XX), gonadal, and hormonal influences (see Chapter 582). The genetic sex of the embryo is determined at fertilization when the gamete pronuclei fuse. The primordial germ cells (oogonia or spermatogonia) migrate from the yolk sac to the gonadal ridges. The primitive gonads are indistinguishable until about the 7th wk of development. Gonadal development determines the progression or regression of the genital ducts and subsequent hormonal production and, thus, the external genitalia. Critical areas in the SRY region (sex-determining region on the Y chromosome) are believed to be the factors that drive the development of a testis from a primitive gonad as well as spermatogenesis. The testis begins to develop between 6 and 7 wk of gestation, first with Sertoli cells followed by Leydig cells, and testosterone production begins at approximately 8 wk of gestation. The genital tract begins to differentiate later than the gonads. The differentiation of the Wolffian ducts begins with an increase in testosterone, and the local action of testosterone activates development of the epididymis, vas deferens, and seminal vesicle. Further male genital duct and external genital structures depend on the conversion of testosterone to dihydrotestosterone.

In a 46,XX embryo, female sexual differentiation occurs about 2 wk later than gonadal differentiation in the male. Because the ovaries develop prior to and separately from the Müllerian ducts, females with Müllerian ductal anomalies usually have normal ovaries and steroid hormone production. The regression of the Wolffian ducts results from the lack of local gonadal testosterone production, and the persistence of the Müllerian (or paramesonephric) ducts results from the absence of antimüllerian hormone (or Müllerian-inhibiting substance) production. The Müllerian ducts continue to differentiate into the fallopian tubes, uterus, and upper vagina without interference from antimüllerian hormone. There are complex interactions among the mesonephric, paramesonephric, and metanephric ducts early in embryonic development, and normal development of the Müllerian system depends on such interaction. If this process is interrupted, coexisting Müllerian and renal anomalies are often discovered in the female patient at the time of evaluation. Differentiation along the female pathway is often referred to as the default pathway, but it is an extremely intricate process regulated by the absence, presence, or dosage compensation of numerous gene products (i.e., SRY, SF-1, WT1, SOX9, Wnt-4, GATA4, DAX-1, BMP4, HOX genes) and remains not entirely understood.

By 10 wk of gestation, the caudal portions of the Müllerian ducts fuse together in the midline to form the uterus, cervix, and upper vagina, in a Y-shaped structure, with the open upper arms of the Y forming the primordial fallopian tubes. Initially the Müllerian ducts are solid cords that gradually canalize as they grow along and cross

<table>
<thead>
<tr>
<th>ANOMALY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolpos</td>
<td>Accumulation of mucus or nonsanguineous fluid in the vagina</td>
</tr>
<tr>
<td>Hemihematometra</td>
<td>Atretic segment of vagina with menstrual fluid accumulation</td>
</tr>
<tr>
<td>Hydrosalpinx</td>
<td>Accumulation of serous fluid in the fallopian tube, often an end result of pyosalpinx</td>
</tr>
<tr>
<td>Didelphic uterus</td>
<td>Two cervices, each associated with 1 uterine horn</td>
</tr>
<tr>
<td>Bicornuate uterus</td>
<td>One cervix associated with 2 uterine horns</td>
</tr>
<tr>
<td>Unicornuate uterus</td>
<td>Result of failure of 1 müllerian duct to descend</td>
</tr>
</tbody>
</table>

Table 554-1 Common Müllerian Anomalies
the mesonephric ducts caudally and fuse in the midline. The mesonephric ducts caudally open into the urogenital sinus, and the müllerian ducts contact the dorsal wall of the urogenital sinus, where proliferation of the cells at the point of contact form the müllerian tubercle. Cells between the müllerian tubercle and the urogenital sinus continue to proliferate, forming the vaginal plate. At the same time of the midline fusion of the müllerian ducts, the medial walls begin to degenerate and resorption occurs to form the central cavity of the uterovaginal canal. Uterine septal resorption is thought to occur in a caudal to cephalad direction and to be complete at approximately 20 wk of gestation. This theory has been scrutinized because some anomalies do not fit the standard classification system. It is possible that septal resorption starts at some point in the middle and proceeds in both directions. At approximately 16 wk of gestation the central cells of the vaginal plate desquamate and resorption occurs, forming the vaginal lumen. The lumen of the vagina is initially separated from the urogenital sinus by a thin hymenal membrane. The hymenal membrane undergoes apoptosis and central resorption and is usually perforate before birth.

EPIDEMIOLOGY
Müllerian anomalies can include abnormalities in portions or all of the fallopian tubes, uterus, cervix, and vagina (Fig. 554-1). True estimates of prevalence are difficult because of the varied presentations and asymptomatic nature of some of the anomalies. Imaging techniques have made significant contributions to uterovaginal anomaly diagnoses, which has increased reporting of anomalies and led to additional combinations of anomalies. Most estimate that müllerian anomalies are present in 2–4% of the female population. The incidence increases in women with a history of adverse pregnancy outcomes or infertility: 5–10% of infertile women undergoing hysterosalpingogram, 5–10% of women with recurrent pregnancy loss, and 25% or more of women with late miscarriages and/or preterm delivery have müllerian defects.

CLINICAL MANIFESTATIONS
Vulvovaginal and müllerian anomalies can manifest at a variety of chronological time points during a female’s life: from infancy, through childhood and adolescence, and adulthood (see Table 554-1). The majority of external genitalia malformations manifest at birth, and often even subtle deviations from normal in either a male or female newborn warrant evaluation. Structural reproductive tract abnormalities can be seen at birth or can cluster at menarche or any time during a woman’s reproductive life. Some müllerian anomalies are asymptomatic, whereas others can cause gynecologic, obstetric, or infertility issues.

Table 554-2 Heritable Disorders Associated with Müllerian Anomalies

<table>
<thead>
<tr>
<th>MODE OF INHERITANCE</th>
<th>DISORDER</th>
<th>ASSOCIATED MÜLLERIAN DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td>Camptobsachydactyly, Hand-foot-genital</td>
<td>Longitudinal vaginal septa, Incomplete müllerian fusion</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>McKusick-Kaufman, Johanson-Blizzard, Renal-genital-middle ear anomalies, Fraser syndrome, Uterine hernia syndrome</td>
<td>Transverse vaginal septa, Longitudinal vaginal septa, Vaginal atresia, Incomplete müllerian fusion, Persistent müllerian duct derivatives</td>
</tr>
<tr>
<td>Polygenic/multifactorial</td>
<td>Mayer-Rokitansky-Küster-Hauser syndrome</td>
<td>Müllerian aplasia</td>
</tr>
<tr>
<td>X-linked</td>
<td>Uterine hernia syndrome</td>
<td>Persistent müllerian duct derivatives</td>
</tr>
</tbody>
</table>

![Figure 554-1](https://example.com/image.png)

Figure 554-1 Classification system of müllerian duct anomalies developed by the American Fertility Society. (From Gholoum S, Puligandla PS, Hui T, et al: Management and outcome of patients with combined vaginal septum, bifid uterus, and ipsilateral renal agenesis [Herlyn-Werner-Wunderlich syndrome]. J Pediatr Surg 41:987–992, 2006, Fig. 3.)
outflow tract obstruction. An adolescent can present with pelvic pain either in association with primary amenorrhea or several months after the onset of menarche. Patients also may be asymptomatic until they present with miscarriage, pregnancy loss, or preterm delivery. When presentation is acutely symptomatic, emergency management may be required. Obstruction can result from a number of distinct anomalies including an imperforate hymen, transverse vaginal septum, and noncommunicating rudimentary horn. As menstrual fluid accumulates proximal to the obstruction, the resulting hematocolpos and hematometra cause cyclic pain or a pelvic mass. Prenatal or neonatal presentation of hydrometrocolpos from distal vaginal obstruction produces fluid accumulation in the vagina and uterus and presents as a lower abdominal mass with or without associated acute urinary tract obstruction. Hydrometrocolpos with polya-dactyly may be a result of 2 disorders: McKusick-Kaufman syndrome (with associated congenital heart disease) and Bardet-Biedl syndrome (with obesity, learning disabilities, retinitis pigmentosa, renal anomalies). Both are autosomal recessive disorders.

Adolescent patients can present with acute obstruction of the outflow tract because of a müllerian anomaly, which requires emergency evaluation and surgical treatment. A small percentage of girls present with concomitant urinary retention caused by an altered urethral angle or pressure on the sacral plexus. Urinary hesitancy and incomplete emptying symptoms may be present before abdominopelvic pain from the obstruction in a patient of any age.

LABORATORY FINDINGS
Several radiographic studies have been used, often in combination, to aid in diagnosis including ultrasound, hysterosalpingogram, sono-hysterography (saline-infusion sonography), and MRI. Laparoscopy and hysteroscopy were the gold standard for evaluation of müllerian anomalies, but the new standard may be MRI because of its noninvasive, high-quality capabilities. MRI is the most sensitive and specific imaging technique used for evaluating müllerian anomalies because it can image nearly all reproductive structures, blood flow, external contours, junctional zone resolution on T2-weighted images, and associated renal and other anomalies. MRI also has a high correlation with surgical findings because of its multiplanar capabilities and high spatial resolution. Three-dimensional ultrasound is another useful diagnostic tool and may be superior to traditional pelvic ultrasound and hysterosalpingogram. Three-dimensional ultrasound and MRI results are highly concordant in the diagnosis of uterine malformations. Evaluation of the external contour of the uterus is important for differentiating types of uterine anomalies. This often requires a combination of radiologic modalities for uterine cavity, external contour, and possible tubal patency. Diagnostic laparoscopy or hysteroscopy may be necessary depending on the presentation, but it is used less with the advancement of MRI and other imaging.

Diagnosis of müllerian anomalies should include a physical exam, pelvic ultrasound, possibly MRI, and renal and skeletal inspections for associated anomalies. Renal anomalies are noted in 30-40% and skeletal anomalies are associated in 10-15% of patients with müllerian anomalies. Unilateral renal agenesis occurs in 15% of patients. The most common skeletal anomalies are vertebral. Patients usually have a normal female karyotype (46,XX), but several familial segregations and gene mutations and/or abnormal karyotypes have been reported (see Table 554-2). Approximately 5-8% of patients with congenital müllerian anomalies have abnormal karyotypes. Most malformations are sporadic, with a polygenic mechanism and multifactorial etiology.

UTERINE ANOMALIES
Anomalous development of the uterus may be symmetric or asymmetric and/or obstructed or nonobstructed. Patients can present with primary amenorrhea or have either irregular or regular menstrual cycles. There may be an asymptomatic pelvic mass or dysmenorrhea. In adolescents and adults, pregnancy loss can cause the first suspicion of a uterine anomaly. Treatment is highly specific to the specific anomaly.

SEPTATE UTERUS
A uterine septum is the most common of all müllerian anomalies, accounting for just over half of all abnormalities, and it is the most common structural uterine anomaly. After the 2 müllerian ducts fuse in the midline, resorption must occur to unify the endometrial cavities; failure of this process results in some degree of uterine septum. It can vary in length from just below the fundus to beyond the cervix, depending on the amount of caudal resorption. A septate uterus has a normal external uterine contour, which is what distinguishes it from a bicornuate or didelphic uterus. An MRI can help delineate between a predominantly fibrous septum and a muscular or myometrial septum. Because the septum may be poorly vascularized, a septate uterus is the most significant anomaly associated with pregnancy loss, as well as other untoward pregnancy outcomes. Hysteroscopic metroplasty (septal excision) is generally recommended in the setting of a previous pregnancy loss. Controversy still exists regarding whether a woman should have such a surgical procedure without a previous pregnancy loss. Correction of uterine septum improves the prognosis in patients with a history of adverse obstetrical outcomes (i.e., spontaneous abortions, preterm delivery). The length of the septum might not correlate with the frequency or occurrence of untoward pregnancy outcomes. Differentiating precisely between bicornuate and septate uteri is extremely important in determining effective and safe treatment plans.

Bicornuate Uterus
Both müllerian ducts develop and elongate in this anomaly, but they do not completely fuse in the midline. The vagina and external cervix are normal, but the extent of division of the 2 endometrial cavities can vary depending on the extent of failed fusion between the cervix and the fundus. Bicornuate uteri are also associated with increased preterm labor and delivery, malpresentation, and miscarriage. This anomaly accounts for approximately 10-20% of müllerian anomalies and a significant percentage of uterine anomalies.

Unicornuate Uterus and Rudimentary Horns
A unicornuate uterus results from a normal creation of a fallopian tube, functional uterus, cervix and vagina from 1 müllerian duct. The other side fails to develop, resulting in either absence of the contralateral müllerian duct or a rudimentary horn. There is a 30-40% association of renal anomalies. If a rudimentary horn is identified, it is important to determine whether functional endometrium is present (usually with T2-weighted MRI images). About two-thirds of rudimentary horns are noncommunicating, some with a fibrous band connecting the 2 structures. Rudimentary horns can also communicate with the contralateral uterus. A fertilized ovum can implant and develop within a rudimentary horn. These pregnancies are incompatible with expectant gestation, and rupture of the horn could be life-threatening. Rupture tends to occur at a later gestation than with an ectopic pregnancy, and hemorrhage is severe. Patients with rudimentary horns without functioning endometrium can also present with pain caused by accumulating menses. Because the other horn has a normal outflow pathway, these patients present with pain, not primary amenorrhea. Pregnancies that arise in a unicornuate uterus are associated with increased preterm labor and delivery, malpresentation, and miscarriage.

Uterine Didelphys
A uterine didelphys is the result of a complete failure of fusion and represents 5% of müllerian anomalies. There are 2 fallopian tubes, 2 completely separate uterine cavities, 2 cervices, and often 2 vaginal canals or 2 partial canals because of an associated longitudinal vaginal septum (75% of the time). Evaluation for renal anomalies should be pursued because they are common as well. At times, the longitudinal septum attaches to 1 sidewall and obstructs 1 side of the vagina (or hemivagina). The combination of uterine didelphys, obstructed hemivagina and ipsilateral
renal anomaly syndrome in the literature. Adolescents with this disorder usually present with abdominal pain shortly after menarche. Although there still may be a risk of adverse pregnancy outcomes with a uterine didelphys (preterm labor, malpresentation), overall pregnancy outcomes are generally good and are associated with less risk than in other uterine anomalies.

Arcuate Uterus
An arcuate uterus is a uterine cavity that has a small midline septum, from lack of a small amount of resorption, and sometimes a slight indentation of the uterine fundus. An arcuate uterus might represent a variant of normal rather than a müllerian anomaly. Untoward pregnancy outcomes are rare and surgical correction is not warranted.

Uterine Anomalies in Diethylstilbestrol-Exposed Patients
Intrauterine diethylstilbestrol (DES) exposure is associated with an increased risk for development of uterine anomalies and clear cell adenocarcinoma of the vagina and cervix. DES was used to prevent preterm delivery, but this practice was discontinued in 1971. Commonly observed uterine features associated with DES exposure include the following: T-shaped uterus, cervical hypoplasia, fallopian tube irregularities, scalloped or irregularly shaped endometrial contour, constriction bands, and others. DES suppresses and/or alters Wnt and HOX genes in mice and thus might work by affecting gene expression involved in müllerian duct development, causing uterine abnormalities, vaginal adenosis, and potentially carcinoma.

Treatment
Treatment depends on the specific anomaly. Hysteroscopic surgical resection is widely supported for uterine septa. If a septate uterus extends through the cervical canal, many choose to leave this cervical portion of the septum because of concerns for future incompetence, although case reports indicate that incisions have been done with uneventful follow-up. Most would support the incision of a uterine septum in the clinical setting of pregnancy loss, but some would also support prophylactic metroplasty without a history of miscarriage, especially before in vitro fertilization.

A noncommunicating horn with functional endometrium should be resected to improve quality of life or prevent future complications; opinions vary as to whether resection of a communicating horn or one with no functional endometrium is warranted. Any surgical resection of a rudimentary horn requires careful surgical technique to protect the ipsilateral ovarian blood supply and the myometrium of the remaining unicorntuate uterus.

Although metroplasty had been advocated with didelphic and bicor-
nuate uteri and a history of poor pregnancy outcomes in the past, currently most clinicians feel there is not enough evidence to support such a complicated procedure. Any obstruction to the outflow tract must also be relieved; this can necessitate creation of a vaginal window or excision of a hemivaginal septum.

VAGINAL ANOMALIES
Abnormalities of the Hymen
An imperforate hymen is the most common obstructive anomaly, and familial occurrences have been reported. Its incidence is most often reported as approximately 1 in 1,000. In the newborn period and early infancy, it may be diagnosed by a bulging membrane caused by a mucocolpos from maternal estrogen stimulation of the vaginal mucosa. This can eventually reabsorb if it is not too large or symptomatic. More often it is diagnosed at the time of menarche, when menstrual fluid accumulates. The clinical manifestations often are a bulging blue-black membrane, pain, primary amenorrhea, and normal secondary sex characters. Depending on the circumstance, patients might have cyclic abdominal pain or a pelvic mass. Other hymenal abnormalities have been reported. A normal hymen can have various configurations (annular, crescentic). Some hymenal membranes do not undergo complete resorption or perforation, resulting in microperforate, cribriform, or septate-shaped hymen. Infants and children vary in age as to when these are recognized, but hymenal anomalies are often discovered after menarche when it is difficult for an adolescent to place a tampon, so resection is indicated.

Congenital Absence of the Vagina and Mayer-Rokitansky-Küster-Hauser Syndrome
Vaginal agenesis or atresia results when the vaginal plate fails to canalize. On physical exam it appears as an extremely foreshortened vagina, sometimes referred to as a vaginal dimple. Isolated (partial) vaginal agenesis involves an area of aplasia between the distal vaginal portion and a normal upper vagina, cervix, and uterus. On initial presentation it may be confused with a low transverse septum or imperforate hymen, and therefore clear delineation of the anomaly is critical before attempting surgical repair. It can also manifest with cyclic pain and a bulging mass just after menarche. Surgical repair and reconstruction are complicated and individualized and best performed with consultation of specialists.

Uterine and vaginal agenesis often occur together because of their close association during development, when müllerian ductal development fails early in the process. The most common cause of vaginal agenesis is Mayer-Rokitansky-Küster-Hauser syndrome, with an incidence reported at 1 in 4,000-10,000 female births. After gonadal dysgenesis, müllerian agenesis is the second most common cause of primary amenorrhea. The cause is unknown and likely has a multigeneic and multifactorial etiology. Mayer-Rokitansky-Küster-Hauser syndrome is characterized by primary amenorrhea, normal vulva, anomalies of the uterus (usually aplasia or agenesis), attenuated fallopian tubes, normal ovaries, normal female karyotype and phenotype, and associated anomalies (most commonly renal and skeletal). The vagina either is completely absent or only has a small dimpled opening. Although most patients with müllerian agenesis have small rudimentary müllerian bulbs, approximately 2-7% of patients can have active endometrium within these uterine structures. These patients will often present with cyclic pelvic pain. MRI imaging is often necessary to determine if any small uterine remnant is present (often located on the pelvic sidewall or near the ovaries and only a small fibromuscular remnant) and to clearly delineate the anomaly. Laparoscopy is not necessary to diagnosis müllerian agenesis but may be useful in the treatment of rudimentary uterine horns, particularly when removal of obstructed uterine structures or associated endometriosis is indicated for pelvic pain. Absence of the vagina and uterus has significant anatomic, physiologic, and psychologic implications for the patient and family. Any diagnosis of müllerian agenesis must be differentiated from androgen insensitivity (testicular feminization) as well; karyotype, serum testosterone levels, and pubic hair distribution usually help distinguish between the two.

Lesions involving other organ systems occur in association with the Mayer-Rokitansky-Küster-Hauser syndrome. The most common are urinary tract anomalies (15-40%) primarily involving unilateral absence of a kidney, a horseshoe or pelvic kidney, and skeletal anomalies (5-10%), which primarily involve vertebral development but can also include hearing impairment.

Longitudinal Vaginal Septa
Longitudinal vaginal septa represent failure of complete canalization of the vagina. These often occur in the presence of uterine anomalies as noted earlier.

Transverse Vaginal Septa (Vertical Fusion Defects)
Vertical fusion defects can result in a transverse septum, which may be imperforate and associated with hematocolpos or hematometra in adolescents or with mucocolpos in infants. These are much less common anomalies, reportedly found in 1 in 80,000 females. Most patients present with amenorrhea and cyclical pain around the time of menarche. Patients who have a small opening in the transverse septa might present with prolonged vaginal drainage and discharge. Transverse vaginal septa vary in location in the vagina (15-20% in the lower third, but most in the middle or upper third of the vagina) and thickness but
are generally ≤1 cm thick. High locations, thick septa, and narrow vaginal orifices present challenging surgical cases.

**Transverse vaginal septa** may be associated with other congenital anomalies, although this occurs less often than with müllerian agenesis. These patients have a functional normal uterus, unlike women with Mayer-Rokitansky-Küster-Hauser syndrome. There is also an increased incidence of endometriosis secondary to retrograde menstruation.

Evaluation of transverse vaginal septa includes careful pelvic examination and often pelvic imaging, usually with MRI and ultrasound, to delineate the anatomic abnormalities. MRI is especially helpful to determine the thickness of the septum and presence of a cervix and for surgical planning. Diagnosis and treatment plans should be made as soon as possible after menarche, because significant accumulation of hematometra and/or hematosalpinx could affect future reproductive success by negatively affecting uterine and/or tubal function.

**Treatment**

An imperforate hymen requires resection to prevent or relieve the outflow tract obstruction. Many approach it with a horizontal, lunate or cruciate incision, excision of excess tissue, and reanastomosis of the mucosal edges. Repair should be done at time of diagnosis, if the patient is symptomatic. Although the lesion may be repaired any time during infancy, childhood, or adolescence, surgery is facilitated by estrogen stimulation and thus is ideally performed in adolescence, either after puberty or menarche. Variants in the hymen with microperforations or hymenal septa may interfere with tampon use and resection of this tissue is usually electively performed.

Treatment of congenital absence of the vagina is usually delayed until the patient is ready to be sexually active. The nonsurgical approach is the most common first-line therapy owing to the high success rate and extremely low morbidity. It requires dedicated use of dilators to create a functional vagina. The series of dilators come in progressively increasing sizes and require a commitment and maturity on the part of the patient to comply with daily use (20-30 min daily). If done correctly it is possible to achieve a functional vaginal length (6-8 cm), width, and physiologic angle for intercourse in about 6-8 wk of therapy. When the ultimate size that accommodates coitus is reached, then the patient must use the dilator or have coitus with a frequency that maintains adequate length.

Surgical approaches require more expertise and often some postoperative vaginal dilation to ensure a functional result. Controversy exists among surgical subspecialties, because pediatric surgeons and pediatric urologists often recommend creating the neovagina in infancy. Pediatric gynecologists and reproductive endocrinologists believe better outcomes result from creating the neovagina when the young woman is interested in sexual activity and can participate in the decision to have surgery and in her own postoperative recovery. There is no consensus as to the best surgical option; the most-used procedures include 2 surgical approaches followed by dilators or an approach using a loop of bowel out of which to construct a vagina. Patients need to be counseled about the ability to use their own oocytes and a gestational carrier through in vitro fertilization to achieve pregnancy. These therapies can be quite complicated physically and emotionally. They are best approached in a multidisciplinary fashion, often with the assistance of psychologic counseling and surgeons with specialized training.

For transverse vaginal septa, treatment is surgical resection of the obstruction through a vaginal approach. Some surgeons advocate waiting for 1 or more menstrual cycles or using preoperative dilators from below to increase the depth and circumference of the distal vagina and to allow menstrual blood to accumulate and dilate the upper portion of the vagina. Complete resection of the septum, with primary anastomosis of the upper and lower mucosal segments, should be attempted. A vaginal stent is sometimes placed postoperatively in the vagina to maintain patency and allow squamous epithelization of the upper vagina and cervix. Follow-up dilatation may be necessary after the stent is removed. Careful preoperative assessment is important because surgeons who begin a case believing they are operating on an imperforate hymen can find themselves in entirely different and more complex surgical planes. Regardless of the approach, vaginoplasty is often best deferred until the patient is mature and physically and psychologically prepared to participate in the healing process and postoperative dilator treatments.

Longitudinal vaginal septa themselves do not lead to adverse reproductive outcomes but may be symptomatic in a patient, causing dyspareunia, difficulties with tampon insertion, or impotence during vaginal birth. Such complaints can warrant a resection of the vaginal septa. In a small number of patients there may be unilateral obstruction of a hemivagina, which would require incision and resection.

**CERVICAL ANOMALIES**

Congenital atresia or complete agenesis of the uterine cervix is extremely rare and often manifests at puberty with amenorrhea and pelvic pain. It is associated with significant renal anomalies in 5-10% of patients. A pelvic MRI is often warranted to completely define the abnormality. Usually, pain and obstruction are significant and a hysterectomy is necessary. Attempts to reconnect the uterus to the vagina are rarely successful and associated with significant morbidity and reoperation rates. As with most müllerian anomalies, the ovaries usually remain normal and future reproduction can still occur through the use of in vitro fertilization and a gestational carrier.

**VULVAR AND OTHER ANOMALIES**

**Complete Vulvar Duplication**

Duplication of the vulva is a rare congenital anomaly that is seen in infancy and consists of 2 vulvas, 2 vaginas, and 2 bladders, a didelphic uterus, a single rectum and anus, and 2 renal systems.

**Labial Asymmetry and Hypertrophy**

With the onset of puberty the labia minora enlarge and grow to an adult size. A woman's labia can vary in size and shape. Asymmetry of the labia, where the right and left labia are different in size and appearance, is a normal variant. Some women are uncomfortable with what they perceive to be their asymmetric or enlarged labia minora and complain about self-consciousness and discomfort while wearing tight clothing, exercising, or having sex. The enlarged labia can have a protuberant and abnormal appearance that can be functionally or psychologically bothersome. Local irritation, problems of personal hygiene with bowel movements or menses, interference with sexual intercourse or while sitting or exercising have resulted in requests for labial reduction. Some surgeons are advertising procedures to reduce uneven or enlarged labia minora. The American College of Obstetricians and Gynecologists does not support performing such surgery unless there is significant impairment in function. Medically indicated surgical procedures can include reversal or repair of female genital cutting and treatment for labial hypertrophy or asymmetrical labial growth secondary to congenital conditions, chronic irritation, or excessive androgenic hormones. Complications of labial surgery include loss of sensation, keloid formation, and dyspareunia.

**Clitoral Abnormalities**

Agenesis of the clitoris is rare. Clitoral duplication has been reported, often associated with pelvic organ abnormalities, including agenesis of other genital tract structures and bladder exstrophy. Exposure to male hormones will result in clitoral enlargement, and is often a sign of a testosterone producing tumor or use of exogenous steroids.

**Cloacal Anomalies**

Cloacal anomalies are rare lesions representing a common urogenital sinus into which the gastrointestinal, urinary, and vaginal canals all exit. Usually there is an abnormality in all or some of the processes of fusion of the müllerian ducts, development of the sinovaginal bulbs, or development of the vaginal plate. The single opening (cloaca) requires surgical correction, preferably by a multidisciplinary pediatric surgical team.

**Ductal Remnants**

Even though the opposite duct regresses in both sexes, there can sometimes be a small portion of either the müllerian or wolffian duct that...
remains in either the male or female, respectively. Such remnants can form cysts, which is what makes them clinically visible during surgery, examination, or imaging. Most do not cause pain, although torsion of some has been reported, and small asymptomatic ones usually do not require resection. The most commonly reported are hydatid of Morgagni cysts (remnant of a Wolffian duct arising from the fallopian tube), cysts of the broad ligament, and Gartner's duct cysts, which can form an ectopic ureter or be found along the cervix or vaginal walls.

*Bibliography is available at Expert Consult.*
Bibliography
Adolescence presents challenges for all children and their families, but particularly so for those with special needs and their families. The start of menstrual periods, the mood changes associated with puberty and the concerns about sexual activity with possible unplanned pregnancies, and worries about safety and abuse may present teens with disabilities and their families with additional issues.

**SEXUALITY AND SEXUAL EDUCATION**

Adolescents with special needs can have physical and/or development disabilities. These young women are often seen as asexual by their families, care providers, and society and therefore sexual education might not have been provided or considered necessary. Physically disabled teens are as likely to be sexually active as nondisabled teens. The care provider needs to assess the teen's knowledge of anatomy and sexuality, her social knowledge of relationships, and her ability to consent to sexual activity. Education regarding HIV and other sexually transmitted infections, disease prevention, and contraception, including postcoital contraception, should be offered at a developmentally appropriate level. Teens with disabilities may be more at risk for isolation and depression during adolescence.

**ABUSE**

The risk for sexual abuse in teens with disabilities is difficult to estimate. Screening for abuse is mandatory. Studies show that teens with physical disabilities are just as sexually active as their nondisabled counterparts but that more of their activity is nonvoluntary. Patients with cognitive impairment are often taught to be cooperative, which may make them more vulnerable. Abuse prevention education can include the No! Go! Tell! model. For teens with limited verbal capacity or developmental delay, abuse may be very hard to detect. The care provider needs to be vigilant in looking for signs on physical exam, such as unexplained bruises or scratches, or changes in behavior, such as regression, which may be indications of sexual abuse in those adolescents (see Chapters 40.1 and 119).

**PELVIC EXAMINATION**

An internal pelvic exam is rarely indicated in teens that are not sexually active, as PapPanicolaou smears are not recommended to start until age 21 yr. An external genital exam can be performed, if there are vulvar issues such as discharge, irregular bleeding, suspicion for abuse, or foreign body. The frog leg position is usually favored over the use of stirrups. If the vagina or cervix needs to be clearly visualized for a medical indication, an exam under anesthesia by a gynecologist should be considered. Testing for sexually transmitted infections can be accomplished by urine testing or vaginal swabs (see Chapter 120).

**MENSTRUATION**

Irregular menstruation is common in teenagers, especially during the 1st 5 yr after menarche, because of immaturity of the hypothalamic–pituitary–ovarian axis and subsequent anovulation (see Chapter 116).

Several conditions in teens with disabilities are associated with an even higher risk of irregular cycles. Teens with Down syndrome have a higher incidence of thyroid disease. There is a higher incidence of reproductive issues, including polycystic ovarian syndrome in teens with epilepsy and on certain antiepileptic drugs (see Chapter 552). Antipsychotic medication can cause hyperprolactinemia, which can affect menstruation.

For teens with disabilities the main issue with menstrual cycles, whether they are regular, irregular, or heavy, is the impact of menstruation on the patient's life, her health, and her ability to perform her normal activities. The history should focus on this aspect, and menstrual calendars may be helpful to document the cycles, behavior, and the impact of treatments. Most adolescents who self-toilet can learn to use menstrual hygiene products appropriately.

The evaluation for abnormal bleeding is the same as for all teens. Areas requiring particular attention for the girl with special needs are the consideration of menstrual suppression for hygiene or cyclic behavioral issues, like crying, tantrums, or withdrawal. A request for birth control, especially coming from a caregiver and not from the teen, requires an evaluation of the teen's ability to consent to sexual activity and evaluate the safety of her environment. Guidelines for abnormal bleeding include menses that are too heavy (in excess of 1 pad/hr for several hours in a row), too long (longer than 10 days), or too frequent (fewer than 20 days apart).

**Treatment of Menstruation**

If after documenting the impact of the regular or irregular cycles on the patient's well-being (often through menstrual or behavioral charting for several months), the care provider, patient, and family decide on menstrual intervention, several options are available. Menstrual regulation is not different from that in the nondisabled teenager in general, although there are some special considerations. Goals for treatment can be to decrease the heaviness of flow, regulate cycles to predictable bleeding, relieve pain or cyclical behavior symptoms, provide contraception, and/or obtain amenorrhea. Menstrual suppression leading to complete amenorrhea is usually difficult to obtain and infrequent scheduled bleeds may be easier to manage than unpredictable spotting, a common side effect of any suppressive treatment, for certain patients. After treatment has started, continue to monitor cycles, ideally with continued menstrual or behavior calendars.

**Nonhormonal Methods**

If menorrhagia or dysmenorrhea (occasionally leading to cyclical behavior changes in nonverbal teens) is the main concern, the patient can be started on nonsteroidal antiinflammatory drugs. These can decrease the flow by up to 20% in adequate doses and can be used alone or in combination with other treatments.

**Estrogen-Containing Methods**

**Oral Contraceptives**

Cyclical oral contraceptives usually lead to regular, lighter cycles with less cramping. Extended cycling through the use of continuous use of oral contraceptives can suppress cycles, with amenorrhea rates improving with time. Some unpredictable spotting is usually unavoidable, and often teens with special needs prefer to have predictable cycles several times a year. A chewable oral contraceptive is available for those with swallowing issues.
**Contraceptive Ring**

The contraceptive ring is usually used in a pattern of 3 wk on and 1 wk off, but it can be used (off-label) in a continuous 4-wk pattern, which can lead to less bleeding. However, the contraceptive ring may be difficult to use for a teen with dexterity problems and help with placement has obvious privacy issues.

**Contraceptive Patch**

The weekly patch can also be used in a continuous fashion. Some teens with developmental disabilities remove their patch erratically, and placement out of reach (e.g., on buttocks or shoulder) is advised.

**Estrogen Use, Venous Thromboembolism and Mobility Issues**

Immobility per se is not a contraindication to estrogen-containing contraceptives, according to the Centers for Disease Control and Prevention medical eligibility criteria for contraception released in 2010. There are some data to support the concern that higher-dose oral estrogen, the combined estrogen patch, and the newer progestin preparations may have a higher risk for venous thromboembolism. However, there are minimal data on the risk of venous thromboembolism in teens with mobility issues in wheelchairs with or without extraneous estrogen. It is important to obtain a thorough and extended family history for hypercoagulability before initiating estrogen therapy. Careful use of lower-dose (30 or 20 μg) ethinyl estradiol preparations may be advisable and third-generation progestin combinations and the patch should only be used if other methods have failed.

**Progesterin-Only Methods**

**Intramuscular Medroxyprogesterone Acetate**

Intramuscular medroxyprogesterone acetate (DMPA) has long been used for menstrual suppression. Two issues are particularly relevant to teens with disabilities. Studies documenting a decrease in bone density associated with longer-term use of DMPA and a black box warning by the FDA have raised concerns about use of these products in young women, although research indicates that the bone density improves after the medication is stopped. For teens with mobility issues or those with very low body weight who are already at risk for low bone density, decreased bone density is a real concern, although the risk of fractures is unclear. Adequate calcium and vitamin D is recommended. The second issue for teens with mobility issues is weight gain associated with DMPA, especially among obese teens, which can lead to transfer and mobility issues. If long-term DMPA is considered for a specific patient, calcium and vitamin D supplementation is recommended and bone density could be measured after several years of use, and weight should be monitored closely.

**Oral Progestins**

Continuous oral progestins can also be very effective to obtain amenorrhea. The progestosterone-only minipill causes significant irregular spotting, so if full suppression is the goal, then other progestins can be used daily, such as norethindrone 2.5 or 5 mg or micronized progesterone 200 mg.

**Progesterone Intrauterine Device**

The 5 yr levonorgestrel-intrauterine device has now been used for many teenagers for contraception as well as heavy menses. Teens with special needs might require anesthesia for insertion if the exam is very difficult because of discomfort, contractures, or a narrow vagina. Checking for strings in a clinic setting may be challenging; however, the intrauterine device location can be confirmed by sonography. There may be a significant amount of irregular bleeding and spotting in the 1st several mo, but there is 20% amenorrhea after insertion and up to 50% amenorrhea after 1 year of use. The bleeding profile of the newer and smaller 3 year progesterone intrauterine device may not be as helpful for menstrual suppression as the amenorrhea rates from the initial studies by the manufacturer are 6% at 1 year, but more studies are needed.

**Implants**

Progesterin subdermal implants have relatively low amenorrhea rates and high rates of unscheduled bleeding and therefore might not be ideal for teens with special needs, as they also require significant patient cooperation for insertion.

**Hormones and Antiepileptic Drugs**

Certain enzyme-inducing seizure medications can interfere with oral contraceptives, change their effectiveness, and/or lead to intermittent bleeding. Higher estrogen dose or shorter injection intervals for DMPA may be considered. The only antiepileptic medication that is affected by combined oral contraceptives is lamotrigine; consequently, the dose of that medication may need to be adjusted if used in conjunction with hormones.

**Surgical Methods**

Surgical procedures such as endometrial ablation, a procedure where the lining of the uterus is surgically removed, and hysterectomy are available for treatment of abnormal periods in adults, but they should only rarely be used in extreme situations for teenagers where all other methods have failed and the patient’s health is severely compromised by her cycles. Endometrial ablation only leads to amenorrhea approximately 30% of the time and has a higher failure rate in women younger than 40 yr of age. Ethical considerations around these methods leading to infertility and consent issues are complicated, and state law varies on this topic.

**CONTRACEPTION**

See also Chapter 117.

The menstrual manipulation methods discussed above can also be used for contraception and if a request for birth control is made, an evaluation of the patient’s ability to consent to sexual activity and the safety of her environment should be done. The method chosen should be the safest method for her situation with the highest protection rate. If she is dependent on others a long-acting reversible contraceptive method may be advisable. Sexually transmitted infections and condom use should be addressed with the teen and specific guidelines on how to obtain condoms and negotiate its use may be needed. A discussion about postcoital contraception is recommended, as well as ways to help the teen obtain this if indicated.

*Bibliography is available at Expert Consult.*

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**555.1 Female Genital Mutilation/Cutting**

*Robert M. Kliegman*

Female genital mutilation/cutting (FGM/C) is a common practice in many parts of the world and is considered a form of child abuse and is illegal in most countries. It is estimated that more than 125 million women in 29 countries have undergone FGM/C (Fig. 555-1). FGM/C breaches international human rights laws and is considered a criminal act.

FGM/C has no health benefit. It threatens the health of girls and women having adverse effects on their psychologic, sexual, and reproductive well-being (Table 555-1). In addition, it increases the risk of HIV infection.

**CLASSIFICATIONS**

Type I: Partial or complete removal of the clitoris, prepuce, or both

Type II: Mutilation or cutting producing partial or complete removal of the clitoris and labia minora with or without excision of the labia majora

Type III: Infibulation; narrowing and sealing of the vaginal orifice by cutting and apposition of the labia minora or majora with or without excision of the clitoris

Type IV: All other harmful procedures
Bibliography
West African women are at greater risk of type II FGM/C, while those in northeast and east Africa and the Middle East are subjected to type III FGM/C. Nonetheless because of migration, women and girls in the United States and Western Europe may undergo FGM/C by traditional practitioners or, rarely, ethnic minority obstetricians or other physicians. Many ethnic women at risk for FGM/C living in the United States or Western Europe are more ambivalent about the procedure demonstrating a conflict between 2 cultures.

**MANAGEMENT**

This is a complex ethnic minority issue that often goes undetected until complications develop, either acutely from the procedure or during pregnancy. Criminalization alone will not eliminate this practice because it is performed in secret, and women are reluctant to discuss this with their healthcare provider, but laws against these procedures are an important step in reducing the number of women subjected to FGM/C.

Surgical repair, such as clitoral reconstruction with removal of scar tissue has been quite beneficial in decreasing pain and enhancing pleasure, including orgasm. Furthermore, women report a positive effect on their self-image and female identity as well as a new sense of “completeness” after reconstructive surgery.

*Bibliography is available at Expert Consult.*
Bibliography
The pituitary gland is the major regulator of an elaborate hormonal system. The pituitary gland receives signals from the hypothalamus and responds by sending pituitary hormones to target glands. The target glands produce hormones that provide negative feedback at the level of the hypothalamus and pituitary (Fig. 556-1). This feedback mechanism enables the pituitary to regulate the amount of hormone released into the bloodstream by the target glands. The pituitary’s central role in this hormonal system and its ability to interpret and respond to a variety of signals have led to its designation as the “master gland.” Table 556-1 lists hypothalamic and pituitary hormones and their functions.

**ANATOMY**

The pituitary gland is located at the base of the skull in a saddle-shaped cavity of the sphenoid bone called the sella turcica. The bony structure protects and surrounds the pituitary bilaterally and inferiorly. The dura, a dense layer of connective tissue, forms the roof of the sella. An external layer of the dura continues into the sella to form its lining. As a result, the pituitary is extradural and is not normally in contact with cerebrospinal fluid. The pituitary gland is connected to the hypothalamus by the pituitary stalk. The pituitary gland is composed of an anterior (adenohypophysis) and a posterior (neurohypophysis) lobe. The anterior lobe constitutes approximately 80% of the gland.

**EMBRYOLOGY**

The anterior pituitary gland originates from the Rathke pouch as an invagination of the oral ectoderm. It then detaches from the oral epithelium and becomes an individual structure of rapidly proliferating cells. By 6 wk of gestation, the connection between the Rathke pouch and the oropharynx is completely obliterated, and the pouch establishes a direct connection with the downward extension of the hypothalamus, which gives rise to the pituitary stalk. Persistent remnants of the original connection between the Rathke pouch and the oral cavity can develop into craniopharyngiomas (see Chapter 497), the most common type of tumor in this area.

**VASCULAR SUPPLY**

The arterial blood supply of the pituitary gland originates from the internal carotid via the inferior, middle, and superior hypophyseal arteries. This network of vessels forms a unique portal circulation connecting the hypothalamus and pituitary. The branches of the superior hypophyseal arteries penetrate the stalk and form a network of vessels that traverse the pituitary stalk and terminate in a network of capillaries within the anterior lobe. It is through this portal venous system that hypothalamic hormones are delivered to the anterior pituitary gland. Anterior pituitary hormones, in turn, are secreted into a secondary plexus of portal veins that drain into the dural venous sinuses.

**ANTERIOR PITUITARY CELL TYPES**

A series of sequentially expressed transcriptional activation factors directs the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. The consequences of mutations in several of these genes are evident in human forms of multiple pituitary hormone deficiency. Five cell types in the anterior pituitary produce 6 peptide hormones. Somatotropes produce growth hormone (GH), lactotropes produce prolactin (PRL), thyrotropes make thyroid-stimulating hormone (TSH), corticotropes express proopiomelanocortin, the precursor of adrenocorticotropic hormone (ACTH), and gonadotropes express luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

**Growth Hormone**

Human GH is a 191-amino-acid single-chain polypeptide that is synthesized, stored, and secreted by somatotropes in the pituitary. Its gene (GH1) is the first in a cluster of 5 closely related genes on the long arm of chromosome 17 (q22-24). The 4 other genes (CS1, CS2, GH2, and CSP) have >90% sequence identity with the GH1 gene.

GH is secreted in a pulsatile fashion under the regulation of hypothalamic hormones. The alternating secretion of growth hormone–releasing hormone, which stimulates GH release, and somatostatin, which inhibits GH release, accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of growth hormone–releasing hormone coincide with troughs of somatostatin. Ghrelin, a peptide produced in the arcuate nucleus of the hypothalamus and in much greater quantities by the stomach, also stimulates GH secretion. In addition to the 3 hypothalamic hormones, physiologic factors play a role in stimulating and inhibiting GH. Sleep, exercise, physical stress, trauma, acute illness, puberty, fasting, and hypoglycemia stimulate the release of GH whereas hyperglycemia, hypothryroidism, and glucocorticoids inhibit GH release.

GH binds to receptor molecules on the surface of target cells. The GH receptor is a 620-amino-acid, single-chain molecule with an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. Proteolytically cleaved fragments of the extracellular domain circulate in plasma and act as a GH-binding protein. As in other members of the cytokine receptor family, the cytoplasmic domain of the GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated Janus kinase (Jak2). Phosphorylation of the kinase and other protein substrates initiates a series of events that leads to alterations in nuclear gene transcription. The signal transducer and activator of transcription 5b (STAT5b) plays a critical role in linking receptor activation to changes in gene transcription.

The biologic effects of GH include increases in linear growth, bone thickness, soft tissue growth, protein synthesis, fatty acid release from adipose tissue, insulin resistance, and blood glucose. The mitogenic actions of GH are mediated through increases in the synthesis of insulin-like growth factor 1 (IGF-1), formerly named somatomedin C, a 70-amino-acid single-chain peptide coded for by a gene on the long arm of chromosome 12. IGF-1 has considerable homology to...
insulin. Circulating IGF-1 is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells, particularly in the growth plates of children, where its effect is exerted by paracrine or autocrine mechanisms. Circulating levels of IGF-1 are related to blood levels of GH and to nutritional status. IGF-1 circulates bound to several different binding proteins. The major one is a 150-kDa complex (IGF-BP3) that is decreased in GH-deficient children. Human recombinant IGF-1 might have therapeutic potential in conditions characterized by end organ resistance to GH such as Laron syndrome and the development of antibodies to administered GH. IGF-2 is a 67-amino-acid single-chain protein that is coded for by a gene on the short arm of chromosome 11. It has homology to IGF-1. Less is known about its physiologic role, but it appears to be an important mitogen in bone cells, where it occurs in a concentration many times higher than that of IGF-1.

**Prolactin**

PRL is a 199-amino-acid peptide made in pituitary lactotropes. The regulation of PRL is unique because PRL is consistently secreted unless it is actively inhibited by dopamine, a peptide produced by neurons in the hypothalamus. Disruption of the hypothalamus or pituitary stalk can result in elevated PRL levels. Dopamine antagonists, states of primary hypothyroidism, administration of thyrotropin-releasing hormone (TRH), and pituitary tumors result in increased serum levels of PRL. Dopamine agonists and processes causing destruction of the pituitary cause reduced levels of PRL.

The primary physiologic role for PRL is the initiation and maintenance of lactation. PRL prepares the breasts for lactation and stimulates milk production postpartum. During pregnancy, PRL stimulates the development of the milk-secretory apparatus, but lactation does not occur because of the high levels of estrogen and progesterone. After delivery, the estrogen and progesterone levels drop and physiologic stimuli such as suckling and nipple stimulation signal PRL release and initiate lactation.

**Thyroid-Stimulating Hormone**

TSH consists of 2 glycoprotein chains (α, β) linked by hydrogen bonding; the α-subunit, which is composed of 89 amino acids and is identical to other glycoproteins (FSH, LH, and human chorionic gonadotropin), and the β-subunit, composed of 112 amino acids, that is specific for TSH.

TSH is stored in secretory granules and released into circulation primarily in response to TRH, which is produced by the hypothalamus. TRH is released from the hypothalamus into the hypothalamic–pituitary portal system and ultimately stimulates TSH release from pituitary thyrotropes. TSH stimulates release of thyroxine (T₄) and triiodothyronine (T₃) from the thyroid gland through the formation of cyclic adenosine monophosphate and the G protein second messenger system. In addition to the negative feedback inhibition by T₃, the release of TRH and TSH is inhibited by dopamine, somatostatin, and glucocorticoids.

Deficiency of TSH results in inactivity and atrophy of the thyroid gland, whereas excess TSH results in hypertrophy and hyperplasia of the thyroid gland.

**Adrenocorticotropic Hormone**

ACTH is a 39-amino-acid single-chain peptide that is derived by proteolytic cleavage from proopiомelanocortin, a 240-amino-acid
prolactin or in the posterior lobe. Arginine vasopressin (antidiuretic hormone) and oxytocin are the 2 hormones produced by neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe. Arginine vasopressin (antidiuretic hormone [ADH]) and oxytocin are the 2 hormones produced by neurosecretion in the hypothalamic nuclei and released from the posterior pituitary. They are octapeptides and differ by only 2 amino acids. They are octapeptides and differ by only 2 amino acids. ADH and its accompanying protein neurophysin II are encoded by the same gene. A single preprohormone is cleaved and the 2 are transported to neurosecretory vesicles in the posterior pituitary. The 2 are released in equimolar amounts.

ADH has a short half-life and responds quickly to changes in hydration. The stimuli for its release are increased plasma osmolality, perceived by osmoreceptors in the hypothalamus, and decreased blood volume, perceived by baroreceptors in the carotid sinus of the aortic arch.

Oxytocin
Oxytocin stimulates uterine contractions at the time of labor and delivery in response to distention of the reproductive tract and stimulates smooth muscle contraction in the breast during suckling, which results in milk letdown. Studies suggest that oxytocin also plays a role in orgasm, social recognition, pair bonding, anxiety, trust, love, and maternal behavior. Most recently, through the interaction with its G-protein-coupled receptor in pancreatic and adipose tissue, oxytocin appears to play a significant role in appetite regulation and obesity by inducing anorexia.

Bibliography is available at Expert Consult.

POSTERIOR PITUITARY CELL TYPES
The posterior lobe of the pituitary is part of a functional unit, the neurohypophysis, that consists of the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe. Arginine vasopressin (antidiuretic hormone [ADH]) and oxytocin are the 2 hormones produced by neurosecretion in the hypothalamic nuclei and released from the posterior pituitary. They are octapeptides and differ by only 2 amino acids.

Antidiuretic Hormone
ADH regulates water conservation at the level of the kidney by increasing the permeability of the renal collecting duct to water. ADH stimulates translocation of water channels through its interaction with vasopressin 2 receptors in the collecting duct, which act through G proteins to increase adenylyl cyclase activity and increase permeability to water. V2 receptors also mediate the von Willebrand factor and tissue plasminogen activator. At higher concentrations, ADH activates V1 receptors in smooth muscle cells and hepatocytes and exerts pressor and glycogenolytic effects through mobilization of intracellular calcium stores. Separate V3 receptors mediate stimulation of ACTH secretion. These effects involve phosphatidylinositol hydrolysis rather than cyclic adenosine monophosphate production.

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Bibliography


Hypopituitarism denotes underproduction of growth hormone (GH) alone or in combination with deficiencies of other pituitary hormones. Affected children have postnatal growth impairment that is specifically corrected by replacement of GH. The incidence of congenital hypopituitarism is thought to be between 1 in 4,000 and 1 in 10,000 live births. With expanding knowledge of the genes that direct pituitary development or hormone production, an increasing proportion of cases can be attributed to specific genetic disorders. Mutations in 7 candidate genes account for 13% of isolated growth hormone deficiency (IGHD) and 20% of multiple pituitary hormone deficiency (MPHD) cases. The likelihood of finding mutations is increased by consanguinity and occurrence in siblings or across generations. The genes, hormonal phenotypes, associated abnormalities, and modes of transmission for such established genetic disorders are shown in Tables 557-1 through 557-4.

Acquired hypopituitarism usually has a later onset and different causes (Table 557-5).

**Multiple Pituitary Hormone Deficiency**

**Genetic Forms**

Sequentially expressed transcriptional activation factors direct the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. Mutations produce different forms of MPHD. *PROP1* and *POU1F1* genes are expressed fairly late in pituitary development only in cells of the anterior pituitary and result in hypopituitarism without anomalies of other organ systems. The *HESX1, LHX3, LHX4,* and *PTX2* genes are expressed at earlier stages and are not restricted to the pituitary. Mutations in these genes tend to produce phenotypes that extend beyond hypopituitarism to include abnormalities in other organs.
Part XXVI ♦ The Endocrine System

Table 557-1  Etiologic Classification of Multiple Pituitary Hormone Deficiency

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<th>GENE OR LOCATION</th>
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<td>R</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>Birth trauma</td>
<td>R</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotrophic hormone; AP, anterior pituitary; D, dominant; EPP, ectopic posterior pituitary; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; MR, mental retardation; PRL, prolactin; R, recessive; TSH, thyroid-stimulating hormone; XL, X-linked.

PROP1

PROP1 is found in the nuclei of somatotropes, lactotropes, and thyrotropes. Its roles include turning on POU1F1 expression, hence its name prophet of PIT1. Mutations of PROP1 are the most common explanation for recessive MPHD and are 10 times as common as the combined total of mutations in other pituitary transcription factor genes. Deletions of 1 or 2 base pairs in exon 2 are most common, followed by missense, nonsense, and splice-site mutations. Anterior pituitary hormone deficiencies are seldom evident in the neonatal period. The median age at diagnosis of GH deficiency is around 6 yr. Recognition of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone, and adrenocorticotropin (ACTH) deficiencies is delayed relative to recognition of GH deficiency. Anterior pituitary size is small in most patients, but in others there is progressive enlargement of the pituitary.

POU1F1 (PIT1)

POU1F1 (formerly PIT1) was identified as a nuclear protein that binds to the GH and prolactin promoters. It is necessary for emergence and mature function of somatotropes, lactotropes, and thyrotropes. Dominant and recessive mutations in POU1F1 are responsible for

Table 557-2  Established Genetic Defects of the GH-IGF Axis Resulting in IGF Deficiency

<table>
<thead>
<tr>
<th>MUTANT GENE</th>
<th>INHERITANCE</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA</td>
<td></td>
<td>Developmental abnormalities</td>
</tr>
<tr>
<td>HESX1</td>
<td>AR</td>
<td>Septooptic dysplasia; variable involvement of pituitary hormones</td>
</tr>
<tr>
<td>PROP1</td>
<td>AR</td>
<td>GH, PRL, TSH, LH, FSH deficiencies; variable ACTH deficiency</td>
</tr>
<tr>
<td>POU1F1 (PIT1)</td>
<td>AR, AD</td>
<td>GH, PRL deficiency; variable degree of TSH deficiency</td>
</tr>
<tr>
<td>RIEG</td>
<td>AD</td>
<td>Rieger syndrome</td>
</tr>
<tr>
<td>LHX3</td>
<td>AR</td>
<td>GH, TSH, LH, FSH, prolactin deficiencies</td>
</tr>
<tr>
<td>LHX4</td>
<td>AD</td>
<td>GH, TSH, ACTH deficiencies</td>
</tr>
<tr>
<td>SOX3</td>
<td>XL</td>
<td>GH deficiency, mental retardation</td>
</tr>
<tr>
<td>GLI2</td>
<td>AD</td>
<td>Holoprosencephaly, hypopituitarism</td>
</tr>
<tr>
<td>GLI3</td>
<td>AD</td>
<td>Pallister-Hall syndrome, hypopituitarism</td>
</tr>
<tr>
<td>GHI1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHHRHR</td>
<td>AR</td>
<td>IGHD, type IB form of IGHD</td>
</tr>
<tr>
<td>GHS-R</td>
<td>AD</td>
<td>GHD and ISS</td>
</tr>
<tr>
<td>GH1</td>
<td>AR</td>
<td>Type IA form of IGHD</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Type IB form of IGHD</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Type II form of IGHD</td>
</tr>
<tr>
<td></td>
<td>XL</td>
<td>Type III form of IGHD; hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Bioactive GH molecule</td>
</tr>
</tbody>
</table>

 ACTH, adrenocorticotrophic hormone (corticotropin); AD, autosomal dominant; ALS, acid labile subunit; AR, autosomal recessive; FSH, follicle-stimulating hormone; GH, growth hormone; GHBP, GH-binding protein; GHD, growth hormone deficiency; GHHRHR, GH-releasing hormone receptor; HPA, hypothalamic pituitary; IGF, insulin-like growth factor; IGHD, isolated GHD, ISS, idiopathic short stature; IUGR, intrauterine growth retardation; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; XL, X-linked.

Table 557-3  Clinical and Biochemical Features of Molecular Defects of the GH–IGF-1 Axis

<table>
<thead>
<tr>
<th>GENE DEFECT/PHENOTYPE</th>
<th>GHR</th>
<th>STAT5B</th>
<th>PTPN11</th>
<th>IGF1</th>
<th>IGFALS</th>
<th>IGFIR</th>
<th>BIOINACTIVE GH</th>
<th>GH1 WITH ANTI-GH ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe growth failure</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mild growth failure</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Midface hypoplasia</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Other facial dysmorphism</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deafness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intellectual delay</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Puberty delay</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IGF-1 deficiency</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IGFBP-3 deficiency</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>ALS deficiency</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>GH excess</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GHBP deficiency</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Homozygous or compound heterozygous mutations</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Heterozygous mutations</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

+, Positive; –, negative; +/-, predominantly positive; –/+, predominantly negative; ALS, acid labile subunit; GH, growth hormone; GHBP, growth hormone–binding protein; IGF, insulin-like growth factor; IGFALS, IGF-1-like activity; IGFIR, IGF-1 receptor.


Table 557-4  Proposed Classification of Growth Hormone Insensitivity

Primary GH insensitivity (hereditary defects)
- GH receptor defect (may be positive or negative for GH-binding protein)
  - Extracellular mutation (e.g., Laron syndrome)
  - Cytoplasmic mutation
  - Intracellular mutation
- GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
  - Stat5b mutations
  - Insulin-like growth factor-1 defects
  - IGF-1 gene deletion
  - IGF-1 transport defect (ALS mutation)
  - IGF-1 receptor defect
- Bioactive GH molecule (responds to exogenous GH)

Secondary GH insensitivity (acquired defects)
- Circulating antibodies to GH that inhibit GH action
- Antibodies to the GH receptor
- GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
- Other conditions that cause GH insensitivity

GH insensitivity syndrome: GH insensitivity associated with the recognizable dysmorphic features described by Laron.

Partial GH insensitivity: GH insensitivity in the absence of dysmorphic features described by Laron.

ALS, acid labile subunit; GH, growth hormone; IGF, insulin-like growth factor.


Complete deficiencies of GH and prolactin and variable TSH deficiency. Affected patients exhibit nearly normal fetal growth but experience severe growth failure in the 1st yr of life. With normal production of LH and follicle-stimulating hormone, puberty develops spontaneously, though at a later than normal age. These patients are not at risk for development of ACTH deficiency. Anterior pituitary size is normal to small.

HESX1
The HESX1 gene is expressed in precursors of all 5 cell types of the anterior pituitary early in embryologic development. Mutations result in a complex phenotype with defects in development of the optic nerve. Heterozygotes for loss-of-function mutations show the combinations of isolated GH deficiency and optic nerve hypoplasia. Homozygotes can have full expression of septooptic dysplasia. This condition combines incomplete development of the septum pellucidum with optic nerve hypoplasia and other midline abnormalities. Clinical observation of nystagmus and visual impairment in infancy leads to the discovery of optic nerve and brain abnormalities. Septooptic dysplasia is associated with anterior and/or posterior pituitary hormone deficiencies in approximately 25% of the cases. These patients often show the triad of a small anterior pituitary gland, an attenuated pituitary stalk, and an ectopic posterior pituitary bright spot. The great majority of patients with septooptic dysplasia do not have HESX1 mutations. The etiology might involve mutations in another gene or a nongenetic explanation (see Chapters 591 and 631).

LHX3 and LHX4
The phenotype produced by recessive loss-of-function mutations of the LHX3 gene resembles that produced by PROP1 mutations. There are
deficiencies of GH, prolactin, TSH, LH, and follicle-stimulating hormone, but not ACTH. Some affected persons show enlargement of the anterior pituitary. The first patients to be described had the usual findings of a short neck and a rigid cervical spine. They were only able to rotate their necks approximately 90 degrees compared with the normal rotation of 150-180 degrees. Dominantly inherited mutations in the structurally similar LHX4 gene consistently produce GH deficiency, with the variable presence of TSH and ACTH deficiencies. Additional findings can include a very small V-shaped pituitary fossa, Chiari I malformation, and an ectopic posterior pituitary.

**Other Congenital Forms**

Pituitary hypoplasia can occur as an isolated phenomenon or in association with more extensive developmental abnormalities such as anencephaly or holoprosencephaly. Midfacial anomalies (cleft lip, palate; see Chapter 310) or the finding of a solitary maxillary central incisor indicates a high likelihood of GH or other anterior or posterior hormone deficiency. At least 12 genes have been implicated in the complex genetic etiology of holoprosencephaly (see Chapter 591.7). The Hall-Pallister syndrome is caused by dominant loss of function mutations in the GLI3 gene. Absence of the pituitary gland is accompanied by hypothalamic hamartoblastoma, polydactyly, nail dysplasia, bifid epiglottis, imperforate anus, and anomalies of the heart, lungs, and kidneys. The combination of anophthalmia and hypopituitarism has been associated with mutations in the SIX6, SOX2, and OTX2 genes.

Severe, early-onset MPHDI including deficiency of ACTH is often associated with the triad of anterior pituitary hypoplasia, absence or attenuation of the pituitary stalk, and an ectopic posterior pituitary bright spot on MRI. Most cases are sporadic and there is a male predominance. Some are from abnormalities of the SOX3 gene, located on the X chromosome. As with septooptic dysplasia, the majority of cases have not been explained at the genetic level.

**Acquired Forms**

Any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary can cause pituitary hormone deficiency (see Table 557-5). Because such lesions are not selective, multiple hormonal deficiencies are usually observed. Diabetes insipidus is more frequent in acquired than in congenital hypopituitarism. The most common lesion is the craniopharyngioma (see Chapter 497). Central nervous system germi-noma, eosinophilic granuloma (histiocytosis), tuberculosis, sarcoid-osis, toxoplasmosis, meningitis, and aneurysms can also cause hypothalamic-hypophysial destruction. Trauma, including abusive head trauma (see Chapter 40), motor vehicle accidents, traction at delivery, anoxia, and hemorrhagic infarction, can also damage the pituitary, its stalk, or the hypophalamus.

**ISOLATED GROWTH HORMONE DEFICIENCY AND INSENSITIVITY**

**Genetic Forms of Growth Hormone Deficiency**

IGHD is caused by abnormalities of the GH-releasing hormone receptor, GH genes, and genes located on the X chromosome.

**Growth Hormone–Releasing Hormone Receptor**

Recessive loss-of-function mutations in the receptor for GH-releasing hormone interfere with proliferation of somatotropes during pituitary development and disrupt the most important signals for release of GH. The anterior pituitary is small, in keeping with the observation that somatotropes normally account for >50% of pituitary volume. There is some compromise of fetal growth followed by severe compromise of postnatal growth.

**GH1**

The GH1 gene is one of a cluster of 5 genes on chromosome 17q22-24. This cluster arose through successive duplications of an ancestral GH gene. Unequal crossing over at meiosis has produced a variety of gene deletions. Small deletions (<10 kb) remove only the GH1 gene, whereas large deletions (45 kb) remove 1 or more of the adjacent genes (CSL, CS1, GH2, and CS2). The growth phenotype is identical with deletion of GH1 alone or GH1 together with 1 or more of the adjacent genes. Loss of the CS1, GH2, and CS2 genes without loss of GH1 causes deficiency of choricionic somatomammotropin and placental GH in the maternal circulation, but it does not result in fetal or postnatal growth retardation. Most children with GH1 gene deletions respond very well to recombinant GH treatment, but some develop antibodies to GH and cease growing.

Recessively transmitted mutations in the GH1 gene produce a similar phenotype. Missense, nonsense, and frameshift mutations have been described. Autosomal dominant IGHD is also caused by mutations in GH1. The mutations usually involve splice-site errors in intron 3 and result in a variant protein that lacks the amino acids normally encoded by exon 3. Accumulation of this protein interferes with the processing, storage, and secretion of the normal GH protein and may result in additional deficiencies of TSH and/or ACTH. There are several reports of mutations in GH1 that lead to variant proteins with reduced biological activity.

**X-Linked Isolated Growth Hormone Deficiency**

Two loci on the X chromosome have been associated with hypopituitarism. The first lies at Xq21.3-q22 in the region of the Bruton thymidine kinase (BTK) gene. Mutations in this region produce hypogammaglobulinemia as well as IGHD. The second locus maps farther out on the long arm, at Xq24-q27.1, a region containing the SOX2 transcription factor gene. Abnormalities in this locus have been linked to IGHD with intellectual disability as well as to MPHDI with the triad of pituitary hypoplasia, missing pituitary stalk, and ectopic posterior pituitary gland.
Acquired Forms
The GH axis is more susceptible to disruption by acquired conditions than are other hypothalamic-pituitary axes. Recognized causes of acquired GH deficiency include the use of radiotherapy for malignancy, meningitis, histiocytosis, and trauma. Children who receive radiotherapy for central nervous system tumors or prevention of central nervous system malignancies (e.g., leukemia) are at risk for developing GH deficiency. Spinal irradiation contributes to disproportionately poor growth of the trunk. Growth typically slows during radiation therapy (see Chapter 718) or chemotherapy (see Chapter 494), improves for 1-2 yr, and then declines with the development of GH deficiency. The dose and frequency of radiotherapy are important determinants of hypopituitarism. GH deficiency is almost universal 5 yr after therapy with a total dose ≥35 Gy. More subtle defects are seen with doses around 20 Gy. Deficiency of GH is the most common defect, but deficiencies of TSH and ACTH can also occur. In contrast to other forms of hypopituitarism, puberty tends to be early rather than delayed (see Chapter 562.3). The clinician is likely to encounter children in the 8-10 yr age range who are growing at rates that are normal for chronological age but subnormal for stage of pubertal development.

GROWTH HORMONE INSENSITIVITY
Abnormalities of the Growth Hormone Receptor
GH insensitivity is caused by disruption of pathways distal to production of GH. Laron syndrome involves mutations of the GH receptor. Children with this condition clinically resemble those with severe IGHD. Birth length tends to be about 1 SD below the mean, and severe short stature with lengths >4 SD below the mean is present by 1 yr of age. Resting and stimulated GH levels tend to be high and insulin-like growth factor (IGF) 1 levels are low. The GH receptor has an extracellular GH-binding domain, a transmembrane domain, and an intracellular signaling domain. Mutations in the extracellular domain interfere with binding of GH. Serum GH-binding protein activity, representing the circulating form of the membrane receptor for GH, is generally low. Mutations in the transmembrane domain can interfere with anchoring of the receptor to the plasma membrane. In these cases, circulating GH-binding protein activity is normal or high. Mutations in the intracellular domain interfere with JAK/STAT signaling.

Postreceptor Forms of Growth Hormone Insensitivity
Some children with severe growth failure, high GH and low IGF-1 levels, and normal GH-binding protein levels have abnormalities distal to the GH binding and activation of the GH receptor. Several have been found to have mutations in the gene encoding signal transducer and activator of transcription 5b (STAT5b). Disruption of this key intermediate connecting receptor activation to gene transcription produces growth failure similar to that seen in Laron syndrome. These patients also suffer from chronic pulmonary infections, consistent with important roles for STAT5b in interleukin cytokine signaling.

IGF-1 Gene Abnormalities
Abnormalities of the IGF-1 gene produce severe prenatal and postnatal growth impairment. Microcephaly, intellectual disability, and deafness are present in patients with exon deletion and a missense mutation. These patients can be expected to respond to recombinant IGF-1 treatment.

Insulin-Like Growth Factor–Binding Protein Abnormalities
Mutation of the gene encoding the acid labile subunit of the circulating 165-kDa IGF-1, IGF-BP3, acid labile subunit complex has been associated with short stature. Total IGF-1 levels were very low. The index case, with homozygosity for an acid labile subunit mutation, did not show an increase in IGF-1 levels or an increase in growth rate during GH treatment.

IGF-1 Receptor Gene Abnormalities
Mutations of the IGF-1 receptor also compromise prenatal and postnatal growth. The phenotype does not appear to be as severe as that seen with absence of IGF-1. Adult heights are closer to the normal range, and affected patients do not have intellectual disability or deafness.

CLINICAL MANIFESTATIONS
Congenital Hypopituitarism
The child with hypopituitarism is usually of normal size and weight at birth, although those with MPHD and genetic defects of the GH1 or GHR gene have birth lengths that average 1 SD below the mean. Children with severe defects in GH production or action typically fall more than 4 SD below the mean for length by 1 yr of age. Those with less-severe deficiencies grow at rates below the 25th percentile for age and gradually diverge from normal height percentiles. Delayed closure of the epiphyses permits growth beyond the normal age when growth should be complete. Features of GH insensitivity are noted in Table 557-6.

Infants with congenital defects of the pituitary or hypothalamus may present with neonatal emergencies such as apnea, cyanosis, or severe hypoglycemia with or without seizures. Prolonged neonatal jaundice is common. It involves elevation of conjugated and unconjugated bilirubin and may be mistaken for neonatal hepatitis. Nystagmus can suggest septooptic dysplasia (see Chapter 591). Microgenia in boys provides an additional diagnostic clue. Deficiency of GH may be accompanied by hypoadrenalinism (see Chapter 575) and hypothyroidism (see Chapter 565) as well as gonadotropin deficiency (see Chapters 583.2 and 586.2).

On physical examination, the head is round and the face is short and broad. The frontal bone is prominent, and the bridge of the nose is depressed and saddle shaped. The nose is small, and the nasolabial folds are well developed. The eyes are somewhat bulging. The mandible and the chin are underdeveloped, and the teeth, which erupt late, are often crowded. The neck is short and the larynx is small. The voice is high-pitched and remains high after puberty. The extremities are well proportioned, with small hands and feet. Weight for height is usually

<table>
<thead>
<tr>
<th>Table 557-6</th>
<th>Clinical Features of Growth Hormone Insensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth and development</td>
<td>Birthweight: near-normal</td>
</tr>
<tr>
<td>Birth length: may be slightly decreased</td>
<td>Postnatal growth: severe growth failure</td>
</tr>
<tr>
<td>Bone age: delayed, but may be advanced relative to height age</td>
<td>Genitalia: micropenis in childhood; normal for body size in adults</td>
</tr>
<tr>
<td>Puberty: delayed 3-7 yr</td>
<td>Sexual function and fertility: normal</td>
</tr>
<tr>
<td>Craniofacies</td>
<td>Hair: sparse before the age of 7 yr</td>
</tr>
<tr>
<td>Forehead: prominent; frontal bossing</td>
<td>Skull: normal head circumference; craniofacial disproportion due to small facies</td>
</tr>
<tr>
<td>Nasal bridge: hypoplastic</td>
<td>Facies: small</td>
</tr>
<tr>
<td>Orbits: shallow</td>
<td>Sclerae: blue</td>
</tr>
<tr>
<td>Dentition: delayed eruption</td>
<td>Voice: high pitched</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>Musculoskeletal/metabolic/miscellaneous</td>
</tr>
<tr>
<td>Hypoglycemia: in infants and children; fasting symptoms in some adults</td>
<td>Walking and motor milestones: delayed</td>
</tr>
<tr>
<td>Hips: dysplasia; avascular necrosis of femoral head</td>
<td>Elbow: limited extensibility</td>
</tr>
<tr>
<td>Skin: thin, prematurely aged</td>
<td>Osteopenia</td>
</tr>
</tbody>
</table>

normal, but an excess of body fat and a deficiency of muscle mass contribute to a pudgy appearance. The genitals are usually small for age, and sexual maturation may be delayed or absent. Facial, axillary, and pubic hair usually is lacking, and the scalp hair is fine. Intelligence is usually normal for age and the children may seem precocious compared to children of a similar size.

Acquired Hypopituitarism

The child is normal initially, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress. When complete or almost complete destruction of the pituitary gland occurs, signs of pituitary insufficiency are present. Atrophy of the adrenal cortex, thyroid, and gonads results in loss of weight, asthenia, sensitivity to cold, mental torpor, and absence of sweating. Sexual maturation fails to take place or regresses if already present. There may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia. Growth slows dramatically. Diabetes insipidus (see Chapter 497) may be present but tends to improve spontaneously with development of central adrenal insufficiency.

If the lesion is an expanding tumor, symptoms such as headache, vomiting, visual disturbances, pathologic sleep patterns, decreased school performance, seizures, polyuria, and growth failure can occur (see Chapter 497). Slowing of growth can antedate neurologic signs and symptoms, especially with craniopharyngiomas. Evidence of pituitary insufficiency may first appear after surgical intervention. In children with craniopharyngiomas, visual field defects, optic atrophy, papilledema, and cranial nerve palsy are common.

LABORATORY FINDINGS

GH deficiency should be suspected in children with severe postnatal growth failure (Table 557-7). Criteria for growth failure include height below the 1st percentile for age and sex or height >2 SD below sex-adjusted mid-parent height. Acquired GH deficiency can occur at any age, and when it is of acute onset, height may be within the normal range. A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity. Observation of low serum levels of IGF-1 and the GH-dependent IGF-BP3 can be helpful, but IGF-1 and IGF-BP3 levels should be matched to normal values for skeletal age rather than chronological age. Values in the upper part of the normal range for age effectively exclude GH deficiency. IGF-1 values in normally growing children and those with hypopituitarism overlap during infancy and early childhood.

Definitive diagnosis of GH deficiency traditionally requires demonstration of absent or low levels of GH in response to stimulation. A variety of provocative tests have been devised that rapidly increase the level of GH in normal children. These include administration of insulin, arginine, clonidine, or glucagon. In chronic GH deficiency, the demonstration of subnormal linear growth, a delayed skeletal age, and low peak levels of GH (<10 ng/mL) in each of 2 provocative tests are compatible with GH deficiency. In acute GH deficiency, a high clinical suspicion of GH deficiency and low peak levels of GH (<10 ng/mL) in each of 2 provocative tests are compatible with GH deficiency. This rather arbitrary cutoff point is higher than the 3 or 5 ng/mL criteria used for diagnosis of adult GH deficiency. There is no consensus regarding adoption of criteria that take into account age, sex, and GH assay characteristics. Some studies indicate that a majority of normal prepubertal children fail to achieve GH values >10 ng/mL with 2 pharmacologic tests. The researchers suggest that 3 days of estrogen priming should be used before GH testing to achieve greater diagnostic specificity.

In addition to establishing the diagnosis of GH deficiency, it is necessary to examine other pituitary functions. Levels of TSH, free thyroxine, ACTH, cortisol, gonadotropins, and gonadal steroids might provide evidence of other pituitary hormonal deficiencies. Antidiuretic hormone deficiency may be established by appropriate studies.

RADIOLOGIC FINDINGS

Conventional x-ray films of the skull have been replaced by CT and MRI. CT is appropriate for recognizing suprasellar calcification associated with craniopharyngiomas and bony changes accompanying histiocytosis. MRI provides a much more detailed view of hypothalamic and pituitary anatomy. Many cases of severe early-onset MPHDS show the triad of a small anterior pituitary gland, a missing or attenuated pituitary stalk, and an ectopic posterior pituitary bright spot at the base of the hypothalamus. Subnormal anterior pituitary height, implying a small anterior pituitary, is common in genetic and idiopathic causes of IGHDS. Craniopharyngiomas are common and pituitary adenomas are rare in children with hypopituitarism. Both hypoplastic and markedly enlarged anterior pituitary glands are seen in patients with PROP1 or LHX3 mutations.

Skeletal maturation is delayed in patients with IGHD and may be even more delayed when there is combined GH and TSH deficiency. Dual-photon x-ray absorptiometry shows deficient bone mineralization, deficiencies in lean body mass, and a corresponding increase in adiposity.

DIFFERENTIAL DIAGNOSIS

The causes of growth disorders are legion. Systemic conditions, such as inflammatory bowel disease, celiac disease, occult renal disease, and anemia, must be considered. Patients with systemic conditions often have greater loss of weight than length. A few otherwise normal children are short (i.e., >3 SD below the mean for age) and grow 5 cm/yr or less but have normal levels of GH in response to provocative tests and normal spontaneous episodic secretion. Most of these children show increased rates of growth when treated with GH in doses comparable to those used to treat children with hypopituitarism. Plasma levels of IGF-1 in these patients may be normal or low. Several groups of treated children have achieved final or near-final adult heights. Different studies have found changes in adult height that range from −2.5 to +7.5 cm compared with pretreatment predictions. There are no methods that can reliably predict which of these children will become
taller in adulthood as a result of GH treatment and which will have compromised adult height.

Diagnostic strategies for distinguishing between permanent GH deficiency and other causes of impaired growth are imperfect. Children with a combination of genetic short stature and constitutional delay of growth have short stature, below-average growth rates, and delayed bone ages. Many of these children exhibit minimal GH secretory responses to provocative stimuli. When children in whom idiopathic or acquired GH deficiency is diagnosed are treated with human GH (hGH) and retested as adults, the majority have peak GH levels within the normal range.

**Constitutional Growth Delay**

Constitutional growth delay is one of the variants of normal growth commonly encountered by the pediatrician. Length and weight measurements of affected children are normal at birth, and growth is normal for the 1st 4-12 mo of life. Height is sustained at a lower percentile during childhood. The pubertal growth spurt is delayed, so their growth rates continue to decline after their classmates have begun to accelerate. Detailed questioning often reveals other family members (often 1 or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature. IGF-1 levels tend to be low for chronological age but within the normal range for bone age. GH responses to provocative testing tend to be lower than in children with a more typical timing of puberty. The prognosis for these children to achieve normal adult height is guarded. Predictions based on height and bone age tend to underestimate eventual height to a greater extent in boys than in girls. Boys with >2 yr of pubertal delay can benefit from a short course of testosterone therapy to hasten puberty after 14 yr of age. The cause of this variant of normal growth is thought to be persistence of the relatively hypogonadotropic state of childhood (see Chapter 15).

**Primary Hypothyroidism**

Primary hypothyroidism (see Chapter 565) is more common than GH deficiency. Low total or free thyroxine and elevated TSH levels establish the diagnosis. Responses to GH provocative tests may be subnormal and the sella may be enlarged. Pituitary hyperplasia recedes during treatment with thyroid hormone. Because thyroid hormone is a necessary prerequisite for normal GH synthesis, it must always be assessed before GH evaluation.

**Psychosocial Causes**

Emotional deprivation is an important cause of retardation of growth and mimics hypopituitarism. The condition is known as *psychosocial dwarfism, maternal deprivation dwarfism, or hyperphagic short stature*. The mechanisms by which sensory and emotional deprivation interfere with growth are not fully understood. Functional hypopituitarism is indicated by low levels of IGF-1 and by inadequate responses of GH to provocative stimuli. Puberty may be normal or even premature. Appropriate history and careful observations reveal disturbed mother-child or family relations and provide clues to the diagnosis (see Chapter 40). Proof may be difficult to establish because the parents or caregivers often hide the true family situation from professionals, and the children rarely divulge their plight. Emotionally deprived children often have perverted or voracious appetites, enuresis, encopresis, insomnia, crying spasms, and sudden tantrums. The subgroup of children with hyperphagia and a normal body mass index tends to show catch-up growth when placed in a less stressful environment.

**TREATMENT**

Recombinant hGH has been available by prescription since 1982. There are currently 8 brands marketed in the United States. They are therapeutically equivalent, with the major differences consisting of proprietary devices for subcutaneous injection and availability of solubilized liquid forms or powders needing reconstitution before injection. At present none of the products are available in long-acting repository forms.

The FDA has approved 8 indications for GH treatment to promote growth. They are GH deficiency, Turner syndrome, chronic renal failure before transplantation, idiopathic short stature, small-for-gestational age short stature, Prader-Willi syndrome, SHOX gene abnormality, and Noonan syndrome. FDA approval for a given indication does not ensure that a patient's third-party insurance carrier will approve payment for the drug. The Pediatric Endocrine Society, the Academy of Pediatrics, and the GH Research Society have published guidelines for hGH treatment of children with classic GH deficiency. Treatment should be started as soon as possible to narrow the gap in height between patients and their classmates during childhood and to harness the greatest effect on mature height. The recommended dose of hGH is 0.18–0.3 mg/kg/wk during childhood. Higher doses have been used during puberty. Recombinant GH is administered subcutaneously in 6 or 7 divided doses. Maximal response to GH occurs in the 1st yr of treatment. Growth velocity during this 1st yr is typically above the 95th percentile for age. With each successive yr of treatment, the growth rate tends to decrease. If growth rate drops below the 25th percentile, compliance should be evaluated before the dose is increased.

Concurrent treatment with GH and a gonadotropin-releasing hormone agonist has been used in the hope that interruption of puberty will delay epiphyseal fusion and prolong growth. This strategy can increase adult height. It can also increase the discrepancy in physical maturity between GH-deficient children and their age peers and can impair bone mineralization. There have also been attempts to forestall epiphyseal fusion in boys by giving drugs that inhibit aromatase, the enzyme responsible for converting androgens to estrogens. Therapy should be continued until near-final height is achieved. Criteria for stopping GH treatment include a decision by the patient that he or she is tall enough, a growth rate <1 inch/yr, and a bone age >14 yr in girls and >16 yr in boys.

Some patients develop either primary or central hypothyroidism while under treatment with GH. Similarly, there is a risk of developing adrenal insufficiency. If unrecognized, this can be fatal. Periodic evaluation of thyroid and adrenal function is indicated for all patients treated with GH.

Recombinant IGF-1 is approved for use in the United States. It is given subcutaneously twice a day. The risk of hypoglycemia is reduced by giving the injections concurrently with a meal or snack. In some situations its use is more efficacious than use of GH. These conditions include abnormalities of the GH receptor and *STAT5b* genes, as well as severe GH deficiency in patients who have developed antibodies to administered GH. Its utility in improving growth rate and adult stature in broader categories of short children is being explored.

The doses of GH used to treat children with classic GH deficiency usually enhance the growth of many non–GH-deficient children as well. Intensive investigation is in progress to determine the full spectrum of short children who may benefit from treatment with GH. The FDA approval for use of GH in idiopathic short stature specifies a height below the 1.2 percentile (~2.25 SD) for age and sex, a predicted height below the 5th percentile, and open epiphyses. Studies of the effect of GH treatment on adult height suggest a median gain of 2-3 inches, depending on dose and duration of treatment.

In children with MPH, replacement should also be directed at other hormonal deficiencies. In TSH-deficient patients, thyroid hormone is given in full replacement doses. In ACTH-deficient patients, the optimal dose of hydrocortisone should not exceed 10 mg/m²/24 hr. Increases of 2-3-fold are made to provide stress coverage during illness or in anticipation of surgical procedures. In patients with a deficiency of gonadotropins, gonadal steroids are given when bone age reaches the age at which puberty usually takes place. For infants with microgenis, 1 or 2 three-month courses of monthly intramuscular injections of 25 mg of testosterone cypionate or testosterone enanthate can bring the penis to normal size without an inordinate effect on osseous maturation.

**COMPLICATIONS AND ADVERSE EFFECTS OF GH TREATMENT**

GH treatment influences glucose homeostasis. Fasting and postprandial insulin levels are characteristically low before treatment, and they normalize during GH replacement. Recent studies indicate that GH...
treatment is associated with a 6-fold increase in the risk for type 2 diabetes and no significant increase in the risk for type 1 diabetes.

Concerns have been raised about the safety of GH treatment in children who become deficient after treatment of brain tumors, leukemia, and other neoplasms. Long-term studies show no increase in risk of recurrence of craniopharyngioma, other brain tumors, or leukemia. At least 3 studies indicate an increased risk of second neoplasms in cancer survivors treated with GH. An unconfirmed study documents a 30% increase in mortality among young adults who received GH in childhood. There appears to be a correlation between risk of mortality and GH doses >0.35 mg/kg/wk.

Other reported side effects include pseudotumor cerebri, slipped capital femoral epiphysis, gynecomastia, and worsening of scoliosis, and in adults treated as a child there is an increased risk of hemorrhagic stroke. The risk of later development of Creutzfeldt-Jakob disease was limited to recipients of contaminated lots of extracted pituitary GH. No comparable risks have been seen with recombinant hGH.

*Bibliography is available at Expert Consult.*
Diabetes insipidus (DI) manifests clinically with polyuria and polydipsia and can result from either vasopressin deficiency (central DI) or vasopressin insensitivity at the level of the kidney (nephrogenic DI). Both central DI and nephrogenic DI can arise from inherited defects of congenital or neonatal onset or can be secondary to a variety of causes (Table 558-1).

**PHYSIOLOGY OF WATER BALANCE**

The control of extracellular tonicity (osmolality) and volume within a narrow range is critical for normal cellular structure and function (see Chapter 55.2). Extracellular fluid tonicity is regulated almost exclusively by water intake and excretion, whereas extracellular volume is regulated by sodium intake and excretion. The control of plasma tonicity and intravascular volume involves a complex integration of endocrine, neural, behavioral, and paracrine systems (Fig. 558-1). Vasopressin, secreted from the posterior pituitary, is the principal regulator of tonicity, with its release largely stimulated by increases in plasma tonicity. Volume homeostasis is largely regulated by the renin–angiotensin–aldosterone system, with contributions from both vasopressin and the natriuretic peptide family.

Vasopressin, a 9-amino-acid peptide, has both antidiuretic and vascular pressor activity and is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is transported to the posterior pituitary via axonal projections, where it is stored awaiting release into the systemic circulation. The half-life of vasopressin in the circulation is 5 min. In addition to responding to osmotic stimuli, vasopressin is secreted in response to significant decreases in intravascular volume and pressure (minimum of 8% decrement) via afferent baroreceptor pathways arising from the aortic arch (carotid sinus) and volume receptor pathways in the cardiac atria and pulmonary veins. Osmotic and hemodynamic stimuli interact synergistically.

The sensation of thirst is regulated by cortical as well as hypothalamic neurons. The thirst threshold is approximately 10 mOsm/kg higher (i.e., 293 mOsm/kg) than the osmotic threshold for vasopressin release. Consequently, under conditions of hyperosmolality, vasopressin is released before thirst is initiated, allowing ingested water to be retained. Chemoreceptors present in the oropharynx rapidly down-regulate vasopressin release following water ingestion.

Vasopressin exerts its principal effect on the kidney via V2 receptors located primarily in the collecting tubule, the thick ascending limb of the loop of Henle, and the periglomerular tubules. The human V2 receptor gene is located on the long arm of the X chromosome (Xq28) at the locus associated with congenital, X-linked, vasopressin-resistant DI. Activation of the V2 receptor results in increases in intracellular cyclic adenosine monophosphate, which leads to the insertion of the aquaporin-2 water channel into the apical (luminal) membrane. This allows water movement along its osmotic gradient into the hypertonic inner medullary interstitium from the tubule lumen and excretion of concentrated urine. In contrast to aquaporin-2,
aquaporin-3 and aquaporin-4 are expressed on the basolateral membrane of the collecting duct cells and aquaporin-1 is expressed in the proximal tubule. These channels may also contribute to urinary concentrating ability.

Atrial natriuretic peptide, initially isolated from cardiac atrial muscle, has a number of important effects on salt and water balance, including stimulation of natriuresis, inhibition of sodium resorption, and inhibition of vasopressin secretion. Atrial natriuretic peptide is expressed in endothelial cells and vascular smooth muscle, where it appears to regulate relaxation of arterial smooth muscle. Atrial natriuretic peptide is also expressed in the brain, along with other natriuretic family members; the physiologic role of these factors has yet to be defined.

**APPROACH TO THE PATIENT WITH POLYURIA, POLYDIPSIA, AND HYPERNATREMIA**

The cause of pathologic polyuria or polydipsia (exceeding 2 L/m²/24 hr) may be difficult to establish in children. Infants can present with irritability, failure to thrive, and intermittent fever. Patients with suspected DI should have a careful history taken, which should quantify the child's daily fluid intake and output and establish the voiding pattern, nocturia, and primary or secondary enuresis. A complete physical examination should establish the patient's hydration status, and the physician should search for evidence of visual and central nervous system dysfunction, as well as for other pituitary hormone deficiencies.

If pathologic polyuria or polydipsia is present, the following should be obtained: serum for osmolality, sodium, potassium, blood urea nitrogen, creatinine, glucose, and calcium; urine for osmolality, specific gravity, and glucose determination. The diagnosis of DI is established if the serum osmolality is >300 mOsm/kg and the urine osmolality is <300 mOsm/kg. DI is unlikely if the serum osmolality is <270 mOsm/kg or the urine osmolality is >600 mOsm/kg. If the patient's serum osmolality is <300 mOsm/kg (but >270 mOsm/kg) and pathologic polyuria and polydipsia are present, a water deprivation test is indicated to establish the diagnosis of DI and to differentiate central from nephrogenic causes.

In the inpatient postneurosurgical setting, central DI is likely if hyperosmolality (serum osmolality >300 mOsm/kg) is associated with urine osmolality less than serum osmolality. It is important to distinguish between polyuria resulting from postneurosurgical central DI and polyuria resulting from the normal diuresis of fluids received intraoperatively. Both cases may be associated with a large volume (>200 mL/m²/hr) of dilute urine, although in patients with DI, the serum osmolality is high in comparison with patients undergoing postoperative diuresis.

**CAUSES OF HYPERNATREMIA**

Hypernatremia is discussed in Chapter 55.3.

**Central Diabetes Insipidus**

Central DI can result from multiple etiologies, including genetic mutations in the vasopressin gene; trauma (accidental or surgical) to vasopressin neurons; congenital malformations of the hypothalamus or pituitary; neoplasms; infiltrative, autoimmune, and infectious diseases affecting vasopressin neurons or fiber tracts; and increased metabolism of vasopressin. In approximately 10% of children with central DI, the etiology is idiopathic. Other pituitary hormone deficiencies may be present (see Chapter 557). Over time, up to 35% of those with idiopathic central DI will develop other hormone deficiencies or have an underlying etiology identified.

Autosomal dominant central DI usually occurs within the 1st 5 yr of life and results from mutations in the vasopressin gene. A number of mutations can cause gene-processing defects in a subset of vasopressin-expressing neurons, which have been postulated to result in endoplasmic reticulum stress and cell death. Wolfram syndrome, which includes DI, diabetes mellitus, optic atrophy, and deafness, also results in vasopressin deficiency. Mutations in 2 genes, which give rise to endoplasmic reticulum proteins, are associated with this condition. Congenital brain abnormalities (see Chapter 591) such as optic nerve hypoplasia syndrome with agenesis of the corpus callosum, the Niikawa-Kuroki syndrome, holoprosencephaly, and familial pituitary hypoplasia with absent stalk may be associated with central DI and defects in thirst perception. Empty sella syndrome, possibly resulting from unrecognized pituitary infarction (see Chapter 557), can be associated with DI in children.

Trauma to the base of the brain and neurosurgical intervention in the region of the hypothalamus or pituitary are common causes of central DI. The triphasic response following surgery refers to an initial phase of transient DI, lasting 12-48 hr, followed by a 2nd phase of syndrome of inappropriate antidiuretic hormone secretion, lasting up to 10 days, which may be followed by permanent DI. The initial phase may be the result of local edema interfering with normal vasopressin secretion; the 2nd phase results from unregulated vasopressin release from dying neurons, whereas in the 3rd phase, permanent DI results if more than 90% of the neurons have been destroyed.

Given the anatomic distribution of vasopressin neurons over a large area within the hypothalamus, tumors that cause DI must either be very large and infiltrative or be strategically located near the base of the hypothalamus, where vasopressin axons converge before their entry into the posterior pituitary. Germinomas and pinealomas typically arise in this region and are among the most common primary brain tumors associated with DI. Germinomas can be very small and undetectable by MRI for several years following the onset of polyuria. Quantitative measurement of α-fetoprotein and β-human chorionic gonadotropin, often secreted by germinomas, should be performed in children with idiopathic or unexplained DI in addition to serial MRI scans. Craniofaryngiomas and optic gliomas can also cause central DI when they are very large, although this is more often a postoperative complication of the treatment for these tumors (see Chapter 497). Hematologic malignancies, such as acute myelocytic leukemia, can cause DI via infiltration of the pituitary stalk and sella.

Langerhans cell histiocytosis (see Chapter 507) and lymphocytic hypophysitis are common types of infiltrative disorders causing central DI, with hypophysitis as the cause in 50% of cases of “idiopathic” central DI. Infections involving the base of the brain (see Chapter 603), including meningitis (meningococcal, cryptococcal, listerial, toxoplasmal), congenital cytomegalovirus infection, and nonspecific inflammatory diseases of the brain may give rise to central DI that is often transient. Drugs associated with the inhibition of vasopressin release include ethanol, phenytoin, opiates, antiangiostatics, halothane, and α-adrenergic agents.

**Nephrogenic Diabetes Insipidus**

Nephrogenic (vasopressin-insensitive) DI (NDI) can result from genetic or acquired causes. Genetic causes are less common but more severe than acquired forms of NDI. The polyuria and polydipsia associated with genetic NDI usually occur within the 1st several wk of life, but may only become apparent after weaning or with longer periods of nighttime sleep. Many infants initially present with fever, vomiting, and dehydration. Failure to thrive may be secondary to the ingestion of large amounts of water, resulting in caloric malnutrition. Long-standing ingestion and excretion of large volumes of water can lead to nonobstructive hydropneophrosis, hydroureter, and megabladde.
**TREATMENT OF CENTRAL DIABETES INSIPIDUS**

**Fluid Therapy**

With an intact thirst mechanism and free access to oral fluids, a person with complete DI can maintain plasma osmolality and sodium in the high normal range, although at great inconvenience. Neonates and young infants are often best treated solely with fluid therapy, given their requirement for large volumes (3 L/m²/24 hr) of nutritious fluid. The use of vasopressin analogs in patients with obligate high fluid intake is difficult given the risk of life-threatening hyponatremia. Although not FDA approved, the use of diluted parenteral and lyophilized long-acting vasopressin analog DDAVP (desmopressin) has been successfully administered to infants with central DI both subcutaneously and orally without causing severe hyponatremia.

**Vasopressin Analogs**

Treatment of central DI in older children is best accomplished with the use of DDAVP. DDAVP is available in an intranasal preparation (onset 5-10 min) and as tablets (onset 15-30 min). The intranasal preparation of DDAVP (10 µg/0.1 mL) can be administered by rhinal tube (allowing dose titration) or by nasal spray. Use of DDAVP oral tablets requires at least a 10-fold increase in the dosage compared with the intranasal preparation. Oral dosages of 25-300 µg every 8-12 hr are safe and effective in children. The appropriate dosage and route of administration is determined empirically based on the desired length of antidiuresis and patient preference. The use of DDAVP nasal spray (10 µg/0.1 mL) for the treatment of primary enuresis in older children should be regarded as a temporizing measure, given it does not affect the underlying condition, and should be used with great caution given the risk of hyponatremia if water intake exceeds the capacity for renal clearance. To prevent water intoxication, patients should have at least 1 hr of urinary breakthrough between doses each day and be advised to drink in response to thirst sensation.

**Aqueous Vasopressin**

Central DI of acute onset following neurosurgery is best managed with continuous administration of synthetic aqueous vasopressin (Pitressin). Under most circumstances, total fluid intake must be limited to 1 L/m²/24 hr during antidiuresis. A typical dosage for intravenous vasopressin therapy is 1.5 mU/kg/hr, which results in a blood vasopressin concentration of approximately 10 pg/mL. On occasion, following hypothalamic (but not transsphenoidal) surgery, higher initial concentrations of vasopressin may be required to treat acute DI, which has been attributed to the release of a vasopressin inhibitory substance. Vasopressin concentrations >1,000 pg/mL should be avoided because they can cause cutaneous necrosis, rhabdomyolysis, cardiac rhythm disturbances, and hypertension. Postneurosurgical patients treated with vasopressin infusion should be switched from intravenous to oral fluids as soon as possible to allow thirst sensation, if intact, to help regulate osmolality.

**TREATMENT OF NEPHROGENIC DIABETES INSIPIDUS**

The treatment of acquired NDI focuses on eliminating, if possible, the underlying disorder, such as offending drugs, hypercalcemia, hypokalemia, or ureteral obstruction. Congenital nephrogenic DI is often difficult to treat. The main goals are to ensure the intake of adequate calories for growth and to avoid severe dehydration. Foods with the highest ratio of caloric content to osmotic load (Na <1 mmol/kg/24 hr) should be ingested to maximize growth and to minimize the urine volume required to excrete the solute load. Even with the early institution of therapy, however, growth failure and developmental disabilities are common.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria. High-dose DDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment could prove useful in patients with genetic defects in the V2 receptor associated with a reduced binding affinity for vasopressin.

*Bibliography is available at Expert Consult.*
Bibliography
Hyponatremia (serum sodium <130 mEq/L) in children is usually associated with severe systemic disorders and is most often a result of intravascular volume depletion, excessive salt loss, or hypotonic fluid overload, especially in infants (see Chapter 55).

The initial approach to the patient with hyponatremia begins with determination of the volume status. A careful review of the patient’s history, physical examination (including changes in weight), and vital signs helps determine whether the patient is hypovolemic or hypervolemic. Supportive evidence includes laboratory data such as serum electrolytes, blood urea nitrogen, creatinine, uric acid, urine sodium, specific gravity, and osmolality (see Chapter 55; Tables 559-1 and 559-2).

<table>
<thead>
<tr>
<th>Table 559-1 Differential Diagnosis of Hyponatremia</th>
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<tr>
<td>DISORDER</td>
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</tr>
<tr>
<td>Systemic dehydration</td>
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<tr>
<td>Decreased effective plasma volume</td>
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<tr>
<td>Primary salt loss (nonrenal)</td>
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<tr>
<td>Primary salt loss (renal)</td>
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<tr>
<td>SIADH</td>
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<tr>
<td>Cerebral salt wasting</td>
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<tr>
<td>Decreased free water clearance</td>
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<tr>
<td>Primary polydipsia</td>
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<td>Runner’s hyponatremia</td>
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<td>NSIAD</td>
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<tr>
<td>Pseudohyponatremia</td>
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<td>Factitious hyponatremia</td>
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NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Clinical Parameters to Distinguish Among SIADH, Cerebral Salt Wasting, and Central Diabetes Insipidus

<table>
<thead>
<tr>
<th>CLINICAL PARAMETER</th>
<th>SIADH</th>
<th>CEREBRAL SAL T WASTING</th>
<th>CENTRAL DI</th>
</tr>
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<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Urine output</td>
<td>Normal or low</td>
<td>High</td>
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<tr>
<td>Urine sodium</td>
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<td>Very high</td>
<td>Low</td>
</tr>
<tr>
<td>Intravascular volume status</td>
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<tr>
<td>Vasopressin level</td>
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<td>Low</td>
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DI, diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

**CAUSES OF HYponATREMIA**

**Syndrome of Inappropriate Antidiuretic Hormone Secretion**

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hyponatremia, an inappropriately concentrated urine (>100 mOsm/kg), normal or slightly elevated plasma volume, normal-to-high urine sodium, and low serum uric acid. SIADH is uncommon in children, and most cases result from excessive administration of vasopressin in the treatment of central diabetes insipidus. It can also occur with encephalitis, brain tumors, head trauma, psychiatric disease, prolonged nausea, pneumonia, tuberculous meningitis, and AIDS and in the postictal phase following generalized seizures. SIADH is the cause of the hyponatremic second phase of the triphasic response seen after hypothalamic–pituitary surgery (see Chapter 558). It is found in up to 35% of patients 1 wk after surgery and can result from retrograde neuronal degeneration with cell death and vasopressin release. Common drugs that have been shown to increase vasopressin secretion or mimic vasopressin action, resulting in hyponatremia, include oxcarbazepine, carbamazepine, chlorpropamide, vinblastine, vincristine, and tricyclic antidepressants.

**Nephrogenic Syndrome of Inappropriate Antidiuresis**

Gain-of-function mutations in the V2 vasopressin receptor gene have been described in male infants presenting with an SIADH-like clinical picture with undetectable vasopressin levels. Activating mutations in the aquaporin-2 gene might also give rise to the same syndrome but have not yet been described.

**Systemic Dehydration**

The initial manifestation of systemic dehydration is often hyponatremia and hyperosmolality, which subsequently lead to the activation of vasopressin secretion and a decrease in water excretion. As dehydration progresses, hypovolemia and/or hypotension become a major stimulus for vasopressin release, further decreasing free water clearance. Excessive free water intake with ongoing salt loss can also produce hyponatremia. Urinary sodium excretion is low (usually <10 mEq/L) owing to a low glomerular filtration rate and concomitant activation of the renin–angiotensin–aldosterone system, unless primary renal disease or diuretic therapy is present.

**Primary Salt Loss**

Hyponatremia can result from the primary loss of sodium chloride as seen in specific disorders of the kidney (congenital polycystic kidney disease, acute interstitial nephritis, chronic renal failure), gastrointestinal tract (gastroenteritis), and sweat glands (cystic fibrosis). The hyponatremia is not solely caused by the salt loss, because the latter also causes hypovolemia, leading to an increase in vasopressin. Mineralocorticoid deficiency (hypoaldosteronism), pseudohypoaldosteronism (genetic or sometimes seen in children with urinary tract obstruction or infection), and diuretics can also result in loss of sodium chloride. Hypoaldosterone states are associated with salt wasting, hypovolemia, hyponatremia, hyperkalemia, and failure to thrive (Table 559-3).

**Decreased Effective Plasma Volume**

Hyponatremia can result from decreased effective plasma volume, as found in congestive heart failure, cirrhosis, nephrotic syndrome, positive pressure mechanical ventilation, severe burns, bronchopulmonary dysplasia in neonates, cystic fibrosis with obstruction, and severe asthma. The resulting decrease in cardiac output leads to reduced water and salt excretion, as with systemic dehydration, and an increase in vasopressin secretion. In patients with impaired cardiac output and elevated atrial volume (congestive heart failure, lung disease), atrial natriuretic peptide concentrations are elevated further, leading to hyponatremia by promoting natriuresis. However, owing to the marked elevation of aldosterone in these patients, their urine sodium remains low (<20 mEq/L) despite this. Unlike dehydrated patients, these patients also have excess total body sodium from activation of the renin–angiotensin–aldosterone system and can demonstrate peripheral edema as well.

**Primary Polydipsia (Increased Water Ingestion)**

In patients with normal renal function, the kidney can excrete dilute urine with an osmolality as low as 50 mOsm/kg. To excrete a daily solute load of 500 mOsm/m², the kidney must produce 10 L/m² of urine per day. Therefore, to avoid hyponatremia, the maximum amount of water a person with normal renal function can consume is 10 L/m². Neonates, however, cannot dilute their urine to this degree, putting them at risk for water intoxication if water intake exceeds 4 L/m²/day (approximately 60 mL/hr in a newborn). Many infants develop transient but symptomatic hyponatremic seizures after being fed pure water without electrolytes rather than breast milk or formula.

**Decreased Free Water Clearance**

Hyponatremia as a consequence of decreased renal free water clearance, even in the absence of an increase in vasopressin secretion, can result from adrenal insufficiency or thyroid deficiency or can be related to a direct effect of drugs on the kidney. Both mineralocorticoids and glucocorticoids are required for normal free water clearance in a vasopressin-independent manner. In patients with unexplained hyponatremia, adrenal and thyroid insufficiency should be considered. In addition, patients with coexisting adrenal failure and diabetes insipidus might have no symptoms of the latter until glucocorticoid therapy unmasks the need for vasopressin replacement. Certain drugs can inhibit renal water excretion through direct effects on the nephron, thus causing hyponatremia; these drugs include high-dose cyclophosphamide, vinblastine, cisplatinum, carbamazepine, and oxcarbazepine.

**Cerebral Salt Wasting**

Cerebral salt wasting appears to be the result of hypersecretion of atrial natriuretic peptide and is seen primarily with central nervous system disorders including brain tumors, head trauma, hydrocephalus, neurosurgery, cerebrovascular accidents, and brain death. Hyponatremia is accompanied by elevated urinary sodium excretion (often >150 mEq/L), excessive urine output, hypovolemia, normal or high uric acid, suppressed vasopressin, and elevated atrial natriuretic...
peptide concentrations (>20 pmol/L). Thus, it is distinguished from SIADH, in which normal or decreased urine output, euvoeina, only modestly elevated urine sodium concentration, and an elevated vasopressin level occur. The distinction between cerebral salt wasting and SIADH is important because the treatment of the 2 disorders differs markedly. However, its existence has been questioned, because few patients with the suspected syndrome have documented hypovolemia and thus might truly have SIADH.

**Runners’ Hyponatremia**

Excess fluid ingestion during long-distance running (e.g., marathon running) can result in severe hyponatremia from hypovolemia-induced activation of arginine vasopressin secretion coupled with excessive water ingestion and is correlated with weight gain, long racing time, and extremes of body mass index.

**Pseudohyponatremia and Other Causes of Hyponatremia**

Pseudohyponatremia can result from hypertriglyceridemia (see Chapter 55). Elevated lipid levels result in a relative decrease in serum water content. As electrolytes are dissolved in the aqueous phase of the serum, they appear low when expressed as a fraction of the total serum volume. As a fraction of serum water, however, electrolyte content is normal. Modern laboratory methods that measure sodium concentration directly, independent of sample volume, do not cause this anomaly. Factitious hyponatremia can result from obtaining a blood sample proximal to the site of intravenous hypotonic fluid infusion.

Hyponatremia is also associated with hyperglycemia, which causes the influx of water into the intravascular space. Serum sodium decreases by 1.6 mEq/L for every 100 mg/dL increment in blood glucose >100 mg/dL. Glucose is not ordinarily an osmotically active agent and does not stimulate vasopressin release, probably because it can equilibrate freely across plasma membranes. In the presence of insulin deficiency and hyperglycemia, however, glucose acts as an osmotic agent, presumably because its normal intracellular access to osmosensor sites is prevented. Under these circumstances, an osmotic gradient exists, stimulating vasopressin release.

**TREATMENT**

Patients with systemic dehydration and hypovolemia should be rehydrated with salt-containing fluids such as normal saline or lactated Ringer solution. Because of activation of the renin–angiotensin–aldosterone system, the administered sodium is avidly conserved, and water diuresis quickly ensues as volume is restored and vasopressin concentrations decrease. Under these conditions, caution must be taken to prevent a too-rapid correction of hyponatremia, which can
result in central pontine myelinolysis characterized by discrete regions of axonal demyelination and the potential for irreversible brain damage.

Hyponatremia from a decrease in effective plasma volume caused by cardiac, hepatic, renal, or pulmonary dysfunction is more difficult to reverse. The most effective therapy is the least easily achieved: treatment of the underlying systemic disorder. For example, patients weaned from positive pressure ventilation undergo a prompt water diuresis and resolution of hyponatremia as cardiac output is restored and vasopressin concentrations decrease. Vaptans represent a new class of small-molecule arginine vasopressin V2 receptor antagonists (aquaretics) useful for the treatment of hypervolemic hyponatremia associated with severe congestive heart failure and chronic liver failure. Although these agents successfully increase plasma sodium, they also lead to increased thirst and plasma vasopressin levels, which can limit their effectiveness.

Patients with hyponatremia from primary salt loss require supplementation with sodium chloride and fluids. Initially, intravenous replacement of urine volume with fluid containing sodium chloride, 150–450 mEq/L depending on the degree of salt loss, may be necessary; oral salt supplementation may be required subsequently. This treatment contrasts with that of SIADH, in which water restriction without sodium supplementation is the mainstay.

Emergency Treatment of Hyponatremia
The development of acute hyponatremia (onset <12 hr) or a serum sodium concentration <120 mEq/L may be associated with lethargy, psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia can cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and can require rapid correction with hypertonic 3% sodium chloride. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to cause an improvement in mental status, and in no case faster than 0.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of Syndrome of Inappropriate Antidiuretic Hormone
Chronic SIADH is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg), a normal daily obligate renal solute load of 500 mOsm/m² would be excreted in 500 mL/m² water. This, plus a daily nonrenal water loss of 500 mL/m², would require that oral fluid intake be limited to 1,000 mL/m²/24 hr to avoid hyponatremia. In young children, this degree of fluid restriction might not provide adequate calories for growth. In this situation, the creation of nephrogenic diabetes insipidus using demeclocycline therapy may be indicated to allow sufficient fluid intake for normal growth. Urea has also been safely used to induce an osmotic diuresis in infants and children.

Treatment of Cerebral Salt Wasting
Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as for the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually due to acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine sodium losses volume for volume.

Bibliography is available at Expert Consult.
Bibliography
Chapter 560

Hyperpituitarism, Tall Stature, and Overgrowth Syndromes

Omar Ali

HYPERPITUITARISM

Primary hypersecretion of pituitary hormones rarely occurs in the pediatric population and should be distinguished from secondary hyperpituitarism, which occurs in the setting of target hormone deficiencies resulting in decreased hormonal feedback, such as in hypogonadism, hypoadrenalism, or hypothyroidism. In secondary hyperpituitarism, chronic pituitary hypersecretion occurs in response to target hormone deficiencies and leads to pituitary hyperplasia, which can enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such enlargements should not be confused with primary pituitary tumors; they disappear when the underlying hormone deficiency is treated. The elevated pituitary hormone levels readily suppress to normal following replacement of end-organ hormones. Pituitary hyperplasia can also occur in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome secondary to corticotropin-releasing hormone excess or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

Primary hypersecretion of pituitary hormones by adenoma is uncommon in childhood. The most commonly diagnosed adenoma during childhood is prolactinoma, followed by corticotropinoma, and then somatotropinoma, which secrete prolactin, corticotropin, and growth hormone, respectively. There are a handful of case reports of thyrotropinoma in children and adolescents. There are no pediatric reports of gonadotropinoma, but hypothalamic hamartomas that secrete excess gonadotropin-releasing hormone are responsible for a significant proportion of cases of precocious puberty.

The monoclonal nature of most pituitary adenomas implies that most originate from a clonal event in a single cell. It is suspected that some pituitary tumors result from stimulation with hypothalamic-releasing hormones and in other instances, as in McCune-Albright syndrome (MAS), the tumor is caused by activating mutations of the GNAS1 gene that codes for the subunit of G\(\alpha\), a guanine nucleotide-binding protein. The clinical presentation typically depends on the pituitary hormone that is hypersecreted. Disruptions of growth regulation and/or sexual maturation are common, as a result of either hormone hypersecretion or local compression by the tumor. MAS also features polyostotic fibrous dysplasia of bone and café-au-lait spots in a distinct distribution.

TALL STATURE

The normal distribution of height predicts that 2.3% of the population will be taller than 2 SD (97.7%) above the mean. The social acceptability and even desirability of tallness (heightism) makes tall stature an uncommon complaint in clinical practice. It is exceptionally unusual for boys and men to seek medical attention regarding excessive height. Girls (or their parents) were historically more likely to approach a physician with concern about tall stature, but even in girls this complaint has become less frequent as tallness has become more acceptable and socially desirable in adult women. Concern about side effects of estrogen treatment and reports of dissatisfaction among adult women subjected to this treatment have also led to a decline in estrogen use.
Differential Diagnosis of Tall Stature and Overgrowth Syndromes

Table 560-1

<table>
<thead>
<tr>
<th>FETAL OVERGROWTH</th>
<th>Differential Diagnosis of Tall Stature and Overgrowth Syndromes</th>
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<tbody>
<tr>
<td>Maternal diabetes mellitus</td>
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<tr>
<td>Cerebral gigantism (Sotos syndrome)</td>
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<tr>
<td>Weaver syndrome</td>
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<td>Beckwith-Wiedemann syndrome</td>
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<tr>
<td>Other IGF-2 excess syndromes</td>
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<td>POSTNATAL OVERGROWTH LEADING TO CHILDHOOD TALL STATURE</td>
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<tr>
<td>Nonendocrine Causes</td>
<td>Family (constitutional) tall stature</td>
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<tr>
<td>Exogenous obesity</td>
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<tr>
<td>Cerebral gigantism (Sotos syndrome)</td>
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<td>Weaver syndrome</td>
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<td>Marfan syndrome</td>
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<td>Fragile X syndrome</td>
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<tr>
<td>Beckwith-Wiedemann syndrome</td>
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<tr>
<td>Klinefelter syndrome (XXY)</td>
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<td>SHOX excess syndromes</td>
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<tr>
<td>Homocystinuria</td>
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<tr>
<td>XYY</td>
<td></td>
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<tr>
<td>Endocrine Causes</td>
<td>Excess GH secretion (pituitary gigantism)</td>
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<td>McCune-Albright syndrome or MEN associated with excess GH secretion</td>
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<tr>
<td>Precocious puberty</td>
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<tr>
<td>Hyperthyroidism</td>
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<tr>
<td>POSTNATAL OVERGROWTH LEADING TO ADULT TALL STATURE</td>
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<tr>
<td>Familial (constitutional) tall stature</td>
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<td>Marfan syndrome</td>
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<td>Klinefelter syndrome (XXY)</td>
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<td>XYY</td>
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<tr>
<td>Androgen or estrogen deficiency or estrogen resistance</td>
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<tr>
<td>Androgen insensitivity syndrome (testicular feminization)</td>
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<tr>
<td>ACTH or cortisol deficiency or resistance</td>
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<tr>
<td>Excess GH secretion (pituitary gigantism)</td>
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</table>

Differential Diagnosis of Tall Stature

Unusual tall stature can have different causes in each group. Table 560-1 lists the causes of tall stature in childhood and adolescence. Figure 560-1 shows an approach to diagnosis.

Overgrowth in the Fetus and Neonate

Maternal diabetes is the most common cause of infants large for gestational age. Even in the absence of clinical symptoms or a family history, the birth of a large-for-gestational-age infant should lead to evaluation for maternal (or gestational) diabetes.

A group of disorders associated with excessive somatic growth and growth of specific organs has been described and is collectively referred to as overgrowth syndromes. These disorders appear to be caused in many cases by excess production and availability of insulin-like growth factor 2 (IGF-2) encoded by the gene IGF2. The best described of these syndromes is the Beckwith-Wiedemann syndrome (BWS), which is an overgrowth malformation syndrome that occurs with an incidence of 1 in 14,000 births, equal in males and females. Approximately 15% of cases are familial, while the rest appear to be sporadic. Most cases of BWS are caused by deregulation of imprinted genes within the chromosome 11p15.5 region. Genetic disruptions affecting this region include gene duplication, loss of heterozygosity, and relaxation or loss of imprinting. The “imprinted” genes involved in BWS and associated childhood tumors include, in addition to IGF2, the gene H19, which is involved in IGF2 suppression, as well as WT-1 (the Wilms tumor gene), cyclin-dependent kinase inhibitor 1C (CDKN1C), potassium channel voltage-gated KQT-like subfamily member 1 (KCQN1), and KCQN1-overlapping transcript 1 (KCQN1OT1, or long QT intronic transcript 1, LIT1).

Affected infants characteristically have macroglossia including macroglossia, hepatosplenomegaly, nephromegaly, and omphalocele. They also have hypoglycemia secondary to hyperinsulinemia as a result of pancreatic β-cell hyperplasia. Children with BWS are predisposed to a specific subset of childhood neoplasms (embryonal tumors), including Wilms tumor, hepatoblastoma, neuroblastoma, and adrenocortical carcinoma. Management focuses on omphalocele, airway issues (a result of macroglossia), and neonatal hypoglycemia. Cancer risk is high until 8 yr of age, and regular surveillance with abdominal ultrasound and measurement of α-fetoprotein is recommended every 3 mo until age 8 yr. Thereafter, renal ultrasound is recommended every 1-2 yr as medullary sponge kidney and nephrocalcinosis may develop later.

Mutations in GPC3, a glycinic gene (which codes for an IGF-2-neutralizing membrane receptor), cause the related Simpson-Golabi-Behmel overgrowth syndrome. Other syndromic causes of fetal overgrowth include Costello syndrome, Weaver syndrome, Sotos syndrome, and Perlman syndrome.

Overgrowth in Childhood or Adolescence

Normal variant, familial, or constitutional tall stature is by far the most common cause of tall stature. Almost invariably, a family history of tall stature can be obtained, and no organic pathology is present. The child is often taller than the child’s peers throughout childhood and enjoys excellent health. The parent of the constitutionally tall adolescent might reflect unhappily upon his or her own adolescence as a tall teenager. There are no abnormalities in the physical examination, and the laboratory studies, if obtained, are negative.

Exogenous obesity is a common condition in adolescence and may be associated with rapid linear growth and early onset of puberty. Bone age is accelerated leading to relative tall stature in childhood but adult height is typically normal.

Klinefelter syndrome (XXY syndrome) is a relatively common (1 in 500-1,000 live male births) abnormality associated with tall stature, learning disabilities (including requirement for speech therapy), gynecomastia, and decreased upper body/lower body segment ratio. Affected boys can have hypotonia, clindactyly, and hypertelorism. The testes are invariably small, although androgen production by Leydig cells is often in the low-normal range. Spermatogenesis and Sertoli cell function are defective, and infertility results. Other genital abnormalities including relatively small phalrus, hypospadia, and cryptorchidism may be present.

XYY syndrome is associated with tall stature, problems in motor and language development, and possible antisocial behavior.

Marfan syndrome is an autosomal dominant connective tissue disorder consisting of tall stature, arachnodactyly, thin extremities, increased arm span, and decreased upper body/lower body segment ratio (see Chapter 702). Additional abnormalities include ocular abnormalities (e.g., lens subluxation), hypotonia, kyphoscoliosis, cardiac valvular deformities, and aortic root dilation.

Homocystinuria is an autosomal recessive inborn error of amino acid metabolism, caused by a deficiency of the enzyme cystathionine synthetase. It is characterized by intellectual disability when untreated, and many of its clinical features resemble Marfan syndrome, particularly ocular manifestations (see Chapter 85).

Sotos Syndrome (Cerebral Gigantism)

Children with cerebral gigantism (also known as Sotos syndrome) are above the 90th percentile for both length and weight at birth; they can also have macrocrania at that time. Most cases of Sotos syndrome are caused by mutations in the NSD1 (nuclear receptor SET domain-containing protein 1) gene, but in the Japanese population most cases are attributable to microdeletions of the 5q35 region that includes this gene. Inheritance is autosomal dominant, but 95% of cases are a result of new mutations. Incidence is estimated to be approximately 1 in 14,000 live births. The NSD1 gene is thought to play a role in epigenetic regulation, but the mechanisms by which mutations lead to the features of Sotos syndrome are not clear at this time.
Although it is characterized by rapid growth, there is no evidence that Sotos syndrome is caused by endocrine dysregulation. A hypothalamic defect has been suggested as a cause, but none has been demonstrated functionally or at necropsy. Growth is markedly rapid; by 1 yr of age, affected infants are taller than the 97th percentile in height. Accelerated growth continues for the 1st 4–5 yr and then returns to a normal rate (see Fig. 560-1). Puberty usually occurs at the expected time but may occur slightly early. Adult height is usually in the upper normal range.

Clinically the syndrome is characterized by a large (macrocephaly) dolichocephalic head, prominent forehead and jaw, hypertelorism, antimongoloid slant of the palpebral fissures, high-arched palate, and large hands and feet with thickened subcutaneous tissue. Clumsiness and awkward gait are also noted, and affected children have great difficulty in sports, in learning to ride a bicycle, and in other tasks requiring coordination. Some degree of developmental disability affects most patients; in some affected children perceptual deficiencies may predominate. Many different types of nonfebrile seizures have been reported and up to 25% of patients with Sotos syndrome have seizures at some point in their life. Affected patients may be at somewhat increased risk for neoplasms, including neuroblastoma, hepatoblastoma, and leukemia, with a lifetime risk of between 2% and 4%. Osseous maturation is usually compatible with the patient's height, although advanced bone age has been reported. Scoliosis develops in up to 30% of cases, usually starting in school-age children. Growth hormone (GH), IGF-1, and other endocrine studies are usually normal; there is no distinctive laboratory or radiologic marker for the syndrome. Abnormal electroencephalograms are common; imaging studies often reveal an enlarged ventricular system, but intracranial pressure is normal. Genetic testing for NSD1 mutations (or fluorescence in situ hybridization for 5q35 microdeletions in Japanese patients) is available and should be routinely used. Management is symptomatic and includes paying special attention to developmental and behavioral problems (which tend to improve with age), scoliosis, and seizure disorder. No specific treatment is needed for the overgrowth itself. There is no consensus on the need for cancer surveillance at this time.

Table 560-2 notes additional features of overgrowth syndromes.

**Hyperthyroidism** in adolescents is associated with rapid growth but normal final adult height. It is almost always caused by Graves disease and is much more common in girls (see Chapter 568).

**Precocious puberty**, whether mediated centrally (increased gonadotropin secretion) or peripherally (increased secretion of androgens or estrogens, or both), results in accelerated linear growth during childhood, mimicking the pubertal growth spurt. Because skeletal maturation is also advanced, adult height is often compromised. Chapter 562 discusses the diagnostic evaluation and management of precocious puberty.

Although **delayed puberty** may be associated with short stature in childhood, as with constitutional delay, failure to eventually enter puberty and complete sexual maturation can result in sustained growth during adult life, with ultimate tall stature. The report of tall stature with open epiphyses resulting from a mutation of the estrogen receptor in a man with normal male sexual maturation underscores the fundamental role of estrogen in promoting epiphyseal fusion and termination of normal skeletal growth. Aromatase deficiency leads to tall stature through similar pathways.

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*Figure 560-1* Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes. Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; SDS, standard deviation score. (From Neylon OM, Werther GA, Sabin MA: Overgrowth syndromes. Curr Opin Pediatr 24:505–511, 2012, Fig. 1, p. 507.)
The purpose of the diagnostic evaluation of tall stature is to distinguish the commonly occurring, normal variant, constitutional variety from the rare pathologic conditions. Often, when the history suggests familial tall stature and the physical examination is entirely normal, no laboratory tests are indicated. It is valuable to obtain a bone age radiograph to be able to predict adult height, which serves as a basis for discussions with the family and for management decisions. If the history suggests any of the aforementioned disorders or the physical examination reveals abnormalities, additional laboratory tests should be obtained. IGF-1 and IGF-binding protein-3 (IGFBP-3) are excellent screening tests for GH excess and can be verified with a glucose suppression test. Laboratory evidence of GH excess mandates MRI evaluation of the pituitary. Chromosome analysis is useful in boys, especially when the ratio of upper to lower body segment is decreased or when developmental disability is present, to rule out Klinefelter syndrome. If Marfan syndrome or homocystinuria is suspected from the physical examination, referral to a cardiologist and an ophthalmologist should be made. Thyroid function tests are

<table>
<thead>
<tr>
<th>GENETIC SYNDROMES</th>
<th>CLINICAL FEATURES</th>
<th>INCIDENCE OF MALIGNANCY (%)</th>
<th>ETIOLOGY</th>
<th>INVESTIGATIONS AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckwith-Wiedemann syndrome*</td>
<td>Hypoglycemia, large tongue, ear pits, omphalocele or umbilical hernia, hemihyperplasia</td>
<td>∼7.5</td>
<td>US heart, kidneys, Chromosomes 11p FISH and/ or MLPA, methylation studies Tumor surveillance justified</td>
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<tr>
<td>Perlman syndrome*</td>
<td>Macrosomia, unusual facies Nephroblastosis</td>
<td>Rare autosomal recessive</td>
<td>US brain (ACC), heart (coarctation), kidneys</td>
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<tr>
<td>Simpson-Golabi- Behmel syndrome*</td>
<td>Coarse facial features, macroGLOSSIA, central groove lower lip, supernumerary nipples</td>
<td>∼7.5 X-linked recessive</td>
<td>US heart, kidney, X-ray spine (vertebral segmentation anomaly) Tumor surveillance justified</td>
<td></td>
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<tr>
<td>Sotos syndrome</td>
<td>Facial gestalt (long, thin face, broad forehead) Feeding difficulties Hypotonia</td>
<td>∼4</td>
<td>US heart, kidneys, Monitor development</td>
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<td>PTEN-hamartoma syndrome (Bannayan- Ruvalcaba-Riley)</td>
<td>Macrocephaly (&gt;97th percentile) often progressive from birth, hypotonia, pigmented skin, penile macules, lipomas</td>
<td>Uncertain</td>
<td>US head, heart, and kidney, Monitor development</td>
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<td>Weaver syndrome</td>
<td>Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, fetal finger pads</td>
<td>∼5-6</td>
<td>US heart, brain, kidney</td>
<td></td>
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<tr>
<td>Marfan syndrome type I</td>
<td>Facial gestalt, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation, lens dislocation</td>
<td>Autosomal dominant fibrin-1 (FBN1)</td>
<td>Eye examination and follow-up Heart US and cardiology follow-up Monitor scoliosis</td>
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<tr>
<td>Marfan syndrome type II or Loeys-Dietz syndrome</td>
<td>Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy</td>
<td>Autosomal dominant, TGF-β pathway anomaly TGFBR1 and TGFBR2 genes</td>
<td>Eye examination usually normal Heart US and follow-up Monitor scoliosis</td>
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</tr>
<tr>
<td>Beals syndrome</td>
<td>Congenital distal arthrogryposis Crumpled ears</td>
<td>Autosomal dominant fibrin-2 (FBN2)</td>
<td>Eye examination and heart US usually normal</td>
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<td>Homocystinuria</td>
<td>Marfan-like habitus Developmental delay Lens dislocation</td>
<td>Autosomal recessive Cystathionine β-synthase (CBS) mutation</td>
<td>Urine metabolic screen Eye examination Monitor development</td>
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<td>Lujan syndrome</td>
<td>Marfanoid habitus plus intellectual disability</td>
<td>X-linked recessive MED12 gene</td>
<td>Eye examination usually normal Heart US usually normal</td>
<td></td>
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<tr>
<td>Sex chromosome aneuploidy Klinefelter 47XXX, 47XY, 47XXX</td>
<td>Tall stature, small testes, gynecomastia Tall stature, ± learning disability</td>
<td>Androgen replacement from puberty in Klinefelter syndrome Monitor development</td>
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<td></td>
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<tr>
<td>Autosomal anomaly Tetrasomy 12p mosaicism,* pat 11pdup, 4pden, 22q13del, 15q26-qter dup</td>
<td>Congenital overgrowth or childhood tall stature with intellectual disability</td>
<td>Monitor development</td>
<td></td>
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</table>

*Overgrowth often presenting at birth. ACC, agenesis of the corpus callosum; FISH, fluorescence in situ hybridization; MLPA, multiple ligation probe amplification; PTEN, phosphatase and tensin homolog; TGF, transforming growth factor; TGFBR, transforming growth factor β receptor; US, ultrasound. From Verge CF, Mowat D: Overgrowth, Arch Dis Child 95:458–463, 2010.
useful to diagnose or rule out hyperthyroidism when this disorder is suspected.

**Treatment of Normal Variant Tall Stature**

Reassurance of the family and the patient is the key to the management of normal variant tall stature. The use of the bone age to predict adult height might provide some comfort for them, as will general supportive discussions on the social acceptability of this condition. Although treatment is possible for girls and boys with excessive growth, its use should be restricted to patients with predicted adult height \( >3.4 \) SD above the mean (79 inches or 200 cm in boys, 73 inches or 185 cm in girls) and evidence of significant psychosocial impairment.

Sex steroids have been used in the treatment of tall stature and are designed to accelerate puberty and to promote epiphyseal fusion; these are therefore of little benefit when given in late puberty. The lack of extensive experience with this form of therapy and the risks of estrogen or androgen treatment for tall stature should be carefully weighed and discussed with the family and treatment should be discouraged except in the most extreme cases. Detailed discussion with the child at the child's level is also advisable as up to 40% of those who underwent such treatments are dissatisfied as adults and feel they were not sufficiently consulted about this course of action. Therapy is initiated ideally before puberty or in early puberty. In boys, treatment should begin before the bone age reaches 14 yr. In the extremely rare instances where treatment is desired, testosterone enanthate is used at a dose of 500 mg intramuscularly every 2 wk for 6 mo. In girls, oral estrogens in various doses have been used to reduce the predicted height, but average height reduction may be only 1.1-2.4 cm. Therapy must begin before the bone age has reached 12 yr. In the rare case where treatment is advised, oral ethinyl estradiol at a dose of 0.15-0.5 mg/day until cessation of growth occurs has been used. Short-term side effects have included benign breast disease, cholelithiasis, hypertension, menstrual irregularities, weight gain, nausea, limb pain, galactorrhea, and thrombosis. Reduced fertility later in life may be a potential long-term complication.

**EXCESS GROWTH HORMONE SECRETION AND PITUITARY GIGANTISM**

In young persons with open epiphyses, overproduction of GH results in *gigantism*; in persons with closed epiphyses, the result is *acromegaly*. Often some acromegalic features are seen with gigantism, even in children and adolescents. After closure of the epiphyses, the acromegalic features become more prominent.

Gigantism is rare, with only several hundred reported cases to date. Most cases are sporadic and are caused by pituitary adenomas or excessive GH-RH secretion by the hypothalamus (and, rarely, by tumors in other parts of the body). *Syndromes associated with pituitary GH excess include* MAS, which is caused by mutations resulting in constitutively activated G-proteins, and can include somatotrophic tumors and excess GH secretion. Approximately 20% of patients with gigantism have MAS (commonly consisting of a triad of precocious puberty, café-au-lait spots, and fibrous dysplasia) and 20% of patients with MAS have some degree of GH hypersecretion. GH-secreting tumors are seen in approximately 60% of patients with *multiple endocrine neoplasia type 1*, but almost all these tumors develop in adult life and cause acromegaly rather than pituitary gigantism. Increased GH secretion and GH-secreting adenomas may also be seen in *neurofibromatosis*, *tuberous sclerosis*, and *Carney complex*.

The cardinal clinical feature of gigantism is longitudinal growth acceleration secondary to GH excess. The usual manifestations consist of coarse facial features and enlarging hands and feet. In young children, rapid growth of the head can precede linear growth. Some patients have behavioral and visual problems. In most recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period in 1 child and at 21 mo of age in another. Giants have rarely been reported to grow to a height of over 8 ft. In some cases the patient may present with local effects of the pituitary tumor (headache, visual field defects, and other pituitary hormone deficiencies) as the main complaint, and there is at least 1 report of a patient presenting with diabetic ketoacidosis induced by GH excess. The presentation of gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults.

Approximately 50% of the pituitary adenomas that cause gigantism also exhibit hyperprolactinemia because they secrete both GH and prolactin. This is because mammosomatotrophs are the most common type of GH-secreting cells involved in childhood gigantism. GH-secreting tumors of the pituitary are typically eosinophilic or chromophobic adenomas. Adenomas can compromise other anterior pituitary function through growth or cystic degeneration. Secretion of gonadotropins, thyrotropin, or corticotropin may be impaired. Delayed sexual maturation or hypogonadism can occur. When GH hypersecretion is accompanied by gonadotropin deficiency, accelerated linear growth can persist for decades. In some cases, the tumor spreads outside the sella, invading the sphenoid bone, optic nerves, and brain. GH-secreting tumors in pediatric patients are more likely to be locally invasive or aggressive than are those in adults.

**Acromegalic features** consist chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. Visual field defects and neurologic abnormalities are common; signs of increased intracranial pressure appear later. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. GH levels are elevated and occasionally exceed 100 ng/mL. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test and IGF-1 and IGFBP-3 levels are consistently elevated in acromegaly and pituitary gigantism.

**Diagnosis**

Most children with tall stature do not have pituitary gigantism and other etiologies of rapid linear growth such as genetic tall stature, precocious puberty, and hyperthyroidism should be carefully excluded. Coexisting findings (e.g., dysmorphic facial features, neurocognitive problems, hemihypertrophy) may suggest syndromic or chromosomal causes of tall stature, such as Sotos, Weaver, Klinefelter, or XYY syndrome. GH hypersecretion can be screened for by testing IGF-1 and IGFBP-3 levels. An excellent linear dose–response correlation between serum IGF-1 levels and 24 hr mean GH secretion has been demonstrated. An elevated IGF-1 level in a patient with appropriate clinical suspicion usually indicates GH excess. Potential confusion can arise in the evaluation of normal adolescents because significantly higher IGF-1 levels occur during puberty than in adulthood, so the IGF-1 level must be age and gender matched. Serum IGFBP-3 levels are also sensitive markers of GH elevations and will be elevated in almost all cases. If IGF-1 and/or IGFBP-3 levels are elevated, then the next step is to test for GH excess by doing an oral glucose-suppression test. The gold standard for the diagnosis of GH excess in adults is the failure to suppress serum GH levels to <1 ng/dL at any time during a 2 hr oral glucose tolerance test with 1.75 g/kg oral glucose challenge (maximum: 75 g). GH levels may not be suppressed to this level in normal adolescents and a cutoff of 5 ng/mL may be more appropriate in this age group. If laboratory findings suggest GH excess, the presence of a pituitary adenoma should be confirmed by MRI of the brain. In rare cases, a pituitary mass is not identified. This might be from an occult pituitary microadenoma or ectopic production of GHRH or GH. CT is acceptable when MRI is unavailable.

**Treatment**

The goals of therapy are to remove or shrink the pituitary mass, to restore GH and secretory patterns to normal, to restore IGF-1 and IGFBP-3 levels to normal, to retain the normal pituitary secretion of other hormones, and to prevent recurrence of disease.

For well-circumscribed pituitary adenomas, transphenoidal surgery is the treatment of choice and may be curative. The tumor should be removed completely. The likelihood of surgical cure depends greatly on the surgeon's expertise as well as on the size and extension of the mass. Intraoperative GH measurements can improve the results of tumor resection. Transphenoidal surgery to resect the tumors is as
safe in children as in adults. At times, a transcranial approach might be necessary. The primary goal of treatment is to normalize GH and IGF-1 levels. GH levels (<1 ng/mL within 2 hr after a glucose load) and serum IGF-1 levels (age-adjusted normal range) are the best tests to define a biochemical cure.

If GH secretion and IGF-1 levels are not normalized by surgery, the options include pituitary irradiation and medical therapy. Further growth of the tumor is prevented by irradiation in >99% of patients. The main disadvantage is the delayed efficacy in decreasing GH levels. GH is reduced by approximately 50% from the initial concentration by 2 yr, by 75% by 5 yr, and approaches 90% by 15 yr. Multiple pituitary hormone deficiency is a predictable outcome, occurring in 40-50% of patients 10 yr after irradiation.

Surgery fails to cure a significant number of patients and radiotherapy may not work fast enough, so medical therapy has an important role in treating patients with GH excess. Treatment is effective and well tolerated with long-acting somatostatin analogs and dopamine agonists, as well as by novel GH antagonists.

The somatostatin analogs are highly effective in the treatment of patients with GH excess. Octreotide suppresses GH to <2.5 ng/mL in 65% of patients with acromegaly and normalizes IGF-1 levels in 70%. The effects of octreotide are well sustained over time. Tumor shrinkage also occurs with octreotide but is generally modest. Consistent GH suppression can be obtained with a continuous SC pump infusion of octreotide or with long-acting formulations, including long-acting octreotide and lanreotide. These produce consistent GH and IGF-1 suppression in acromegalic patients with once-monthly or biweekly IM depot injections. These sustained-release preparations have not been formally tested in children. Octreotide injection in the pediatric population has been used at doses of 1-40 µg/kg/24 hr. In adults the long-acting form is used in a dose of 10-40 mg every mo, but no pediatric dose range has been established.

For patients with both GH and prolactin oversecretion, dopamine agonists, such as bromocriptine and cabergoline, which bind to pituitary dopamine type 2 receptors and may also suppress GH secretion, should be considered. Prolactin levels are often adequately suppressed, but GH levels and IGF-1 levels are rarely normalized with this treatment modality alone. Tumor shrinkage occurs in a minority of patients. The effectiveness of these agents may be additive to that of octreotide. Cabergoline therapy at doses of 0.25-4.0 mg/wk (given 1-2 times per wk) has been used in adults with acromegaly, and because of its less-frequent dosing and lower incidence of side effects as compared to bromocriptine, this is now considered the dopamine agonist of choice in both adults and children. Side effects can include nausea, vomiting, abdominal pain, arrhythmias, nasal stuffiness, orthostatic hypotension, sleep disturbances, and fatigue.

Pegvisomant is a GH receptor antagonist that competes with endogenous GH for binding to the GH receptor. It effectively suppresses GH and IGF-1 levels in patients with acromegaly caused by pituitary tumors as well as ectopic GHRR hypersecretion. Normalization of IGF-1 levels occurs in up to 90% of patients treated daily with this drug for 3 mo or longer. The adult dosage is 10-40 mg via subcutaneous injection once daily, although twice-weekly protocols have also been reported as highly successful. IGF-1 levels and hepatic enzymes must be monitored. Combined therapy with somatostatin analogs and weekly pegvisomant injections also is effective. Pediatric experience is limited, but case reports indicate that it can successfully suppress IGF-1 levels when used in doses of 10-30 mg/day.

Prolactinoma
Prolactin-secreting pituitary adenomas are the most common pituitary tumors in adolescents. With the advent of MRI, more of these tumors, particularly microadenomas (<1 cm in diameter), are being detected. The most common presenting manifestations are headache, primary or secondary amenorrhea, and galactorrhea. The disorder affects more than twice as many girls as boys; most patients have undergone normal puberty before becoming symptomatic. Only a few have delayed puberty. In some kindreds with type I multiple endocrine neoplasia, prolactinomas are the presenting feature during adolescence.

Prolactin levels may be elevated mildly (40-50 ng/mL) or markedly (10,000-15,000 ng/mL). Most prolactinomas in children are large (macroadenomas), cause the sella to enlarge, and in some cases cause visual field defects. Approximately 30% of patients with macroadenomas develop other pituitary hormone deficiencies, particularly GH deficiency. Alternatively, prolactin-secreting adenomas might also stain for and secrete excess GH and/or thyroid-stimulating hormone. Prolactinomas should not be confused with the hyperprolactinemia and pituitary hyperplasia that can occur in patients with primary hypothyroidism, which is readily treated with thyroid hormone (see Chapter 565). Moderate elevations (<200 ng/mL) of prolactin are also associated with a variety of medications (antipsychotics, metoclopramide, phenothiazines, verapamil), with pituitary stalk dysfunction such as can occur with craniospharyngioma, with chronic stress (rarely >40 ng/mL), and with nipple stimulation.

In some cases, extreme hyperprolactinemia is associated with a “hook effect” that leads to factiously low values on blood tests. In cases where clinical features are compatible with hyperprolactinemia, serial dilution of the lab specimen should be done to rule out this kind of measurement error. On the other hand, patients may have factiously elevated prolactin levels on immunoassay as a result of the presence of prolactin polymers and dimers (macroprolactinemia). In cases where an elevated prolactin is detected in an asymptomatic patient, unnecessary diagnostic work-up and treatment can be avoided by performing polyethylene glycol precipitation to exclude the presence of macroprolactinemia, which is clinically benign.

In most patients where the hyperprolactinemia is secondary to an adenoma, it can be effectively treated with dopamine agonists. Treatment leads to lowering of prolactin levels and tumor shrinkage in the vast majority of patients. Because of its greater efficacy and lower incidence of side effects, cabergoline is considered the drug of choice for treatment of hyperprolactinemia in doses ranging from 0.125-1.0 mg twice weekly. Higher doses may be needed in some patients but carry the risk of inducing cardiac valvular abnormalities and should be carefully monitored.

When dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or the size of the adenoma, and when symptoms or signs attributable to hyperprolactinemia or adenoma size persist during treatment, transphenoidal surgery should be considered.

Corticotropinoma
Corticotropinoma is very rare in children, and its peak occurrence is at age 14 yr. Cushing disease refers specifically to an adrenocorticotropic hormone–producing pituitary adenoma that stimulates excess cortisol production and secretion. It is more common than primary adrenal causes of Cushing syndrome, except in younger children (younger than 5 yr of age), in whom adrenal carcinomas and adrenal activating mutations of MAS are rare but dominant causes of the syndrome. Adenomas causing Cushing disease are almost always microadenomas with a diameter of <5 mm and are significantly smaller than all other types of adenomas at presentation. The most sensitive indicator of excess glucocorticoid secretion in children is growth failure, which generally precedes other manifestations. Patients develop weight gain that tends to be centripetal rather than generalized. Pubertal arrest, hypertension, large purplish striae, fatigue, and depression are also common. In prepubertal children, males are more frequently affected than females.

Midnight salivary cortisol measurements can be used as a screening test for cortisol excess, but confirmation requires at least 1 additional test (either 24 hr urinary free cortisol or an overnight dexamethasone suppression test). Location of the microadenoma is usually determined by MRI, and bilateral inferior petrosal sinus sampling may be needed in difficult cases. Transphenoidal surgery is the treatment of choice for Cushing disease in children. Initial remission rates of 70-98% of patients and long-term success rates of 50-98% are reported. Residual transient hypoadrenalism is often observed after surgery, lasting as...
long as 30 mo. Pituitary radiotherapy is used if cortisol levels remain elevated and/or adrenocorticotropic hormone levels continue to be detectable. Successful treatment may not correct the height deficit, and GH deficiency may be present after treatment and should be treated as required.

Bibliography is available at Expert Consult.
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Between early childhood and approximately 8-9 yr of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in girls, testosterone in boys). One to 3 yr before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep–entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin–releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among hypothalamus, pituitary, and gonads in the peripubertal period. By midpuberty, LH pulses become evident even during the daytime and occur at approximately 90–120 min intervals. A second critical event occurs in middle or late adolescence in girls in whom cyclicility and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The resulting “GnRH pulse generator” is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, and neurokinin-B (stimulatory) and γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). GnRH secretion is also regulated by factors produced by the glial cells, such as transforming growth factor α. Loss-of-function mutations of the KISS1 R—also known as GPR54—gene (the gene encoding a G-protein–coupled receptor whose ligand is kisspeptin) cause an autosomal recessive form of hypogonadotropic hypogonadism, whereas gain-of-function mutations of the gene are associated with precocious puberty. Increased transforming growth factor α signaling is associated with the occurrence of central precocious puberty in patients with hypothalamic hamartoma.

The interpretation of the hormonal changes of puberty is complex. Issues in interpreting LH and follicle-stimulating hormone measurements include the presence of multiple gonadotropin isoforms, immunoassay–related variability, and problems inherent to their pulsatile secretion, which mandates serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland, and serum LH concentrations tend to increase earlier in the course of the pubertal process in boys than in girls. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 yr of age, before any increase in LH or sex hormones and before the earliest physical changes of puberty are apparent; this process is called adrenarche. DHEAS is the most abundant adrenal C-19 steroid in the blood, and its serum concentration remains fairly stable over 24 hr. A single measurement of this hormone is commonly used as a marker of adrenal androgen secretion. Although adrenarche typically antedates the onset of gonadal activity (gonadarche) by a few years, the 2 processes do not seem to be causally related, because adrenarche and gonadarche are dissociated in conditions such as central precocious puberty and adrenocortical failure.

The effects of gonadal steroids (testosterone in boys, estradiol in girls) on bone growth and osseous maturation are critical. Both aromatase deficiency and estrogen receptor defects result in delayed epiphyseal fusion and tall stature in affected males. These observations suggest that estrogens, rather than androgens, are responsible for the process of bone maturation that ultimately leads to epiphyseal fusion and cessation of growth. Estrogens also mediate the increased production of growth hormone, which along with a direct effect of sex steroids on bone growth, is responsible for the pubertal growth spurt.

The age of onset of puberty varies and is more closely correlated with osseous maturation than with chronological age (see Chapter 14). In females, the breast bud (thelarche) is usually the first sign of puberty (10–11 yr of age), followed by the appearance of pubic hair (pubarche) 6–12 mo later. The interval to the onset of menstrual activity (menarche) is usually 2–2.5 yr, but may be as long as 6 yr. In the United States, at least 1 sign of puberty is present in approximately 95% of girls by 12 yr of age and in 99% of females by 13 yr of age. Peak height velocity occurs early (at breast stages II–III, typically between 11 and 12 yr of age) in girls and always precedes menarche. The mean age of menarche is approximately 12.75 yr. There are, however, wide variations in the sequence of changes involving growth spurt, breast bud, pubic hair, and maturation of the internal and external genitalia.

In males, growth of the testes (>24 mL in volume or 2.5 cm in longest diameter) and thinning of the scrotum are the first signs of puberty (11–12 yr). These are followed by pigmentation of the scrotum and growth of the penis (see Chapter 14) and by pubarche. Appearance of axillary hair usually occurs in midpuberty. In males, unlike in females, acceleration of growth begins after puberty is well under way and is maximal at genital stages IV–V (typically between 13 and 14 yr of age). In males, the growth spurt occurs approximately 2 yr later than in females, and growth may continue beyond 18 yr of age.

Genetic and environmental factors affect the timing for the onset of puberty. Population-based studies in the United States and in Europe suggest secular trends for earlier onset of puberty over the past few decades in females and, to a lesser degree, in males. African–American and, to a lesser extent, Hispanic girls appear to be more advanced in the development of secondary sex characteristics for age than white females. The timing of menarche has, however, remained generally stable with only a marginal advancement (2.5–4 mo) reported in U.S.-based studies and no significant change reported in the Copenhagen Puberty Study. The latter also showed that the earlier onset of breast development observed in girls examined in 2006–2008 when compared to those seen in 1991–1993 (means: 10.88 yr vs 9.86 yr, p < 0.0001) was not associated with different levels of estradiol or gonadotropins when girls of similar chronological ages were compared between the 2 groups. Hence, earlier breast development may not necessarily reflect an earlier activation of the hypothalamic–pituitary–gonadal axis but could be the consequence of other factors such as increased adiposity or increased exposure to certain environmental agents. Positive correlations between the degree of adiposity and earlier pubertal development in girls have, indeed, been reported. Conversely, female athletes in whom leanness and strenuous physical activity have coexisted from early childhood frequently exhibit a marked delay in puberty or menarche, and they frequently have oligomenorrhea or amenorrhea as adults (see Chapter 691). Pubertal delay is also prevalent in males who are physically very active. These observations support the thesis that the energy balance is closely related to the activity of the GnRH pulse generator and the mechanisms initiating and sustaining puberty via hormonal signals such as leptin or other adipokines.

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Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 yr in girls and 9 yr in boys. The variation in the age of the onset of puberty in normal children, particularly of different ethnicities, makes this definition somewhat arbitrary. It remains in use by most clinicians.

Depending on the primary source of the hormonal production, precocious puberty may be classified as central (also known as gonadotropin dependent, or true) or peripheral (also known as gonadotropin independent or precocious pseudopuberty) (Table 562-1). Central precocious puberty is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation. In peripheral precocious puberty, some of the secondary sex characteristics appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (contrasexual) (see Chapters 583-588).

Peripheral precocious puberty can induce maturation of the hypothalamic-pituitary-gonadal axis and trigger the onset of central puberty. This mixed type of precocious puberty occurs commonly in conditions such as congenital adrenal hyperplasia, McCune-Albright syndrome, and familial male-limited precocious puberty, when the bone age reaches the pubertal range (10.5-12.5 yr).

562.1 Centrally Precocious Puberty

Central precocious puberty is defined by the onset of breast development before the age of 8 yr in girls and by the onset of testicular development (volume ≥4 mL) before the age of 9 yr in boys, as a result of the early activation of the hypothalamic-pituitary-gonadal axis. It occurs 5-10-fold more frequently in girls than in boys and is usually sporadic. A high prevalence of idiopathic central precocious puberty has been reported in girls adopted from developing countries, with the limitation that the exact date of birth may be uncertain.

Although approximately 90% of girls have an idiopathic form, a structural central nervous system (CNS) abnormality can be demonstrated in up to 75% of boys with central precocious puberty. Beyond its etiology, which thus needs to be specifically addressed, central precocious puberty can impact linear growth and affect the child’s growth potential.

**CLINICAL MANIFESTATIONS**

Sexual development may begin at any age and generally follows the sequence observed in normal puberty. In girls, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported as early as 5.5 yr of age (Fig. 562-1). In boys, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed as early as 5-6 yr of age. In affected girls and boys, height, weight, and osseous maturation are advanced. The increased rate of bone maturation results in early closure of the epiphyses, and the ultimate stature is less than it would have been otherwise. Without treatment, approximately 30% of girls and an even larger percentage of boys achieve a height less than the 5th percentile as adults. Mental development is usually compatible with chronological age. Emotional behavior and mood swings are common, but serious psychologic problems are rare.

Although the clinical course is variable, 3 main patterns of pubertal progression can be identified. Most girls (particularly those younger than 6 yr of age at the onset) and a large majority of boys have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential. An increasing percentage of girls (older than 6 yr of age at the onset with an idiopathic form) have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. Spontaneously regressive or unsustained central precocious
puberty is quite rare. This variability in the natural course of sexual precocity underscores the need for longitudinal observation at the onset of sexual development, before treatment is considered.

**LABORATORY FINDINGS**

Sex hormone concentrations are usually appropriate for the stage of puberty in both sexes. Despite the availability of sensitive and specific (liquid chromatography/tandem mass spectrometry) assays for sex hormones, serum estradiol concentrations are low or undetectable in the early phase of sexual precocity in girls, as they are in normal puberty. In boys, serum testosterone levels are usually detectable or clearly elevated by the time the parents seek medical attention, provided that an early morning blood sample is obtained. With the use of highly sensitive immunofluorometric and chemiluminescent assays, serum luteinizing hormone (LH) concentrations are undetectable in prepubertal children in random blood samples, but become detectable in 50-75% of girls and a higher percentage of boys with central sexual precocity. Unfortunately, a number of hospitals use only moderately sensitive immunoenzymatic assays for LH, and often insensitive assays for estradiol and testosterone, which decrease the diagnostic sensitivity of these measurements. Measurement of LH in serial blood samples obtained during sleep has greater diagnostic power than measurement in a single random sample, and it typically reveals a well-defined pulsatile secretion of LH. Intravenous administration of gonadotropin-releasing hormone (GnRH stimulation test) or a GnRH agonist (leuprolide stimulation test) is a helpful diagnostic tool, particularly for boys, in whom a "pubertal" LH response (LH peak >5 IU/L) with predominance of LH over follicle-stimulating hormone (FSH) tends to occur early in the course of precocious puberty. In girls with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast stages II to early III (immunometric LH peak, <5 IU/L), and the LH:FSH ratio may remain low until mid-advanced puberty. In such girls with "low" LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL), 20-24 hr after stimulation with leuprolide.

**Osseous maturation** is variably advanced, often by more than 2-3 SD. Pelvic ultrasonography in girls reveals progressive enlargement of the ovaries, followed by enlargement of the fundus and then of the whole uterus to pubertal size. An MRI scan usually demonstrates physiologic enlargement of the pituitary gland, as seen in normal puberty; it may also reveal CNS pathology (see Chapter 562.2).

**DIFFERENTIAL DIAGNOSIS**

Organic CNS causes of central sexual precocity are more likely in boys, and those girls who have rapid breast development, have estradiol
>30 pg/mL, or are younger than 6 yr of age. All children in these categories should undergo MRI scans of the brain and pituitary gland. Specific criteria for ordering brain imaging in girls older than age 6 yr are still lacking, although some authorities recommend MRI scans for all children with central precocious puberty.

**Gonadotropin-independent** causes of iatrogenic sexual precocity must be considered in the differential diagnosis (see Table 562-1). For girls, these include tumors of the ovaries, autonomously functioning ovarian cysts, feminizing adrenal tumors, McCune-Albright syndrome, and exogenous sources of estrogens. In boys, congenital adrenal hyperplasia, adrenal tumors, Leydig cell tumors, chorionic gonadotropin-producing tumors, exposure to exogenous androgens, and familial male precocious puberty should be considered.

**TREATMENT**

Virtually all boys and the large subgroup of girls with rapidly progressive precocious puberty are candidates for treatment. Girls with slowly progressive idiopathic central precocious puberty do not seem to benefit in terms of height prognosis from GnRH-agonist therapy. Former small-for-gestational-age infants may be at greater risk of short stature as adults and may require more aggressive treatment of precocious puberty, possibly in conjunction with human growth hormone therapy. Certain patients require treatment solely for psychologic or social reasons, including children with special needs and very young girls at risk of early menarche.

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for treatment of central precocious puberty. By virtue of being more potent, and having a longer duration of action, than native GnRH, these GnRH agonists (after a brief period of stimulation) “desensitize” the gonadotropic cells of the pituitary to the stimulatory effect of endogenous GnRH and effectively halt the progression of central sexual precocity.

Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentrations of the drug for weeks or months, constitute the preparations of choice for treatment of central precocious puberty. In the United States, the available preparations include: (1) leuprolide acetate (Lupron Depot-Ped), in a dose of 0.25-0.3 mg/kg (minimum 7.5 mg) intramuscularly once every 4 wk; (2) longer-acting preparations of depot leuprolide, allowing for injections (11.25-30.0 mg intramuscularly) every 90 days; and (3) histrelin (Supprelin LA), a subcutaneous 50 mg implant with effects lasting 12 mo. Other preparations (D-Trp6-GnRH [Decapeptyl], goserelin acetate [Zoladex]) are approved for treatment of precocious puberty in other countries. Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1-3% of patients treated with depot leuprolide. Breakage or malfunction of the histrelin implant is very rare. Other available treatment options, usually reserved for children who cannot tolerate the products listed above, include subcutaneous injections of aqueous leuprolide, given once or twice daily (total dose 60 μg/kg/24 hr), or intranasal administration of the GnRH agonist nafarelin (Synarel), 800 μg bid. The potential for irregular compliance with daily administration, as well as the variable absorption of the intranasal route for nafarelin, may limit the long-term benefit of the latter preparations on adult height. GnRH antagonists have not been investigated sufficiently and are not FDA approved. Oral GnRH antagonists are also being investigated.

Treatment results in decrease of the growth rate, generally to age-appropriate values, and an even greater decrease of the rate of osseous maturation. Some children, particularly those with greatly advanced (pubertal) bone age, may show marked deceleration of their growth rate and a complete arrest in the rate of osseous maturation. Treatment results in enhancement of the predicted height, although the actual adult height of patients followed to epiphyseal closure is approximately 1 SD less than their midparental height. In girls, breast development may regress in those with Tanner stages II-III development. Most commonly, the size of the breasts remains unchanged in girls with stages III-V development, or may even increase slightly because of progres-
should be considered for patients with associated growth hormone deficiency.

Precocious Puberty Following Irradiation of the Brain

Wassim Chemaitilly and Luigi R. Garibaldi

Radiation therapy, generally for leukemia or intracranial tumors, increases the risk of precocious puberty considerably, whether the irradiation is directed to the hypothalamic area or to areas of the brain anatomically distant from the hypothalamus. Low-dose radiation (18-24 Gy) hastens the onset of puberty almost exclusively in girls. High-dose radiation (25-47 Gy), conversely, appears to trigger precocious sexual development in both sexes, and the risk of sexual precocity is inversely proportional to the age of the child at the time radiation was given. This type of sexual precocity is often associated with growth hormone deficiency and may be masked by the growth-promoting effect of the increased sex hormone levels.

TREATMENT

Regardless of the cause, therapy with GnRH agonists is as effective in children with organic brain lesions causing central precocious puberty, and these analogs are the therapy of choice to halt premature sexual development. This includes patients with a hypothalamic hamartoma, if precocious puberty is its only manifestation. In patients with hypothalamic hamartoma and associated intractable gelastic or psychomotor seizures, however, stereotactic radiation therapy (gamma knife surgery) is effective and less risky than neurosurgical intervention.

For other neurologic lesions, therapy depends on the nature and location of the pathologic process. Combined growth hormone therapy should be considered for patients with associated growth hormone deficiency.

562.3 Precocious Puberty Following Irradiation of the Brain

Wassim Chemaitilly and Luigi R. Garibaldi

Radiation therapy, generally for leukemia or intracranial tumors, increases the risk of precocious puberty considerably, whether the irradiation is directed to the hypothalamic area or to areas of the brain anatomically distant from the hypothalamus. Low-dose radiation (18-24 Gy) hastens the onset of puberty almost exclusively in girls. High-dose radiation (25-47 Gy), conversely, appears to trigger precocious sexual development in both sexes, and the risk of sexual precocity is inversely proportional to the age of the child at the time radiation was given.

This type of sexual precocity is often associated with growth hormone deficiency and may also be combined with other conditions (spinal irradiation, hypothyroidism) adversely affecting the prognosis for a reasonable adult height. Unless careful attention is paid to early signs of pubertal development in these children, the combination of growth hormone deficiency and the growth-promoting effect of sex steroids often results in a "normal" growth rate at the expense of a rapidly advancing bone age and impaired adult height potential.

TREATMENT

GnRH analogs are effective in arresting pubertal progression in this patient population. However, concomitant growth hormone deficiency (and/or thyroid hormone deficiency) should be diagnosed and treated promptly in order for the adult height prognosis to improve.
Paradoxically, hypopituitarism with gonadotropin deficiency may subsequently develop as a late effect of high-dose CNS irradiation in patients with or without a history of precocious puberty, and it may require substitution therapy with sex steroids.

**562.4 Syndrome of Precocious Puberty and Hypothyroidism**

Luigi R. Garibaldi and Wassim Chemaitilly

In children with untreated hypothyroidism, the onset of puberty is usually delayed until epiphyseal maturation reaches 12-13 yr of age. Precocious puberty in a child with untreated hypothyroidism and a prepubertal bone age presents a strikingly unphysiologic association, yet is common and may occur in as many as 50% of children with severe hypothyroidism of long duration. These children have the usual manifestations of hypothyroidism, including retardation of growth and of osseous maturation (see Chapter 565). The cause of the hypothyroidism is usually Hashimoto thyroiditis, which often goes undiagnosed, especially in children with special needs such as those with trisomy 21, in whom the symptoms of profound hypothyroidism may be more difficult to recognize. Sexual development in girls consists of breast enlargement and menstrual bleeding; the latter may occur even in girls with minimal breast enlargement. Pelvic sonography may reveal large, multicystic ovaries. Boys have testicular enlargement associated with modest or no penile enlargement. No pubic hair development occurs. No pubic hair development occurs in either girls or boys. Enlargement of the sella, which is typical of long-standing primary hypothyroidism, may be demonstrated by skull film or MRI. Plasma levels of thyroid-stimulating hormone (TSH) are markedly elevated, often greater than 500 μU/ml, and those of prolactin and estradiol are mildly elevated. Although serum FSH is low and LH is undetectable, when measured by specific assays, the markedly elevated concentrations of TSH appear to interact with the FSH receptor (“specificity spillover”), thus inducing FSH-like effects in the absence of LH effects on the gonads. The FSH-like effect suffices to induce estradiol secretion by the ovaries, while in boys testicular enlargement occurs without substantial testosterone secretion. Thus, the precocious puberty associated with hypothyroidism behaves as an incomplete form of gonadotropin-dependent puberty. Treatment of the hypothyroidism results in rapid return to normal of the biochemical and clinical manifestations. Possible progression to central puberty with rapid bone age advancement could occur in the months following the initiation of thyroid hormone replacement, a complication that would justify delaying puberty with GnRH analogs. Macroorchidism (testicular volume >30 mL) may persist in adult males despite adequate levothyroxine therapy.

**562.5 Chorionic Gonadotropin-Secreting Tumors**

Luigi R. Garibaldi and Wassim Chemaitilly

These are rare tumors, whose secretion of hCG stimulates the LH receptors in the Leydig cells. The testicles are only minimally enlarged, and the histology reveals interstitial cell hyperplasia with no spermatogenesis. Plasma levels of testosterone are elevated, while those of FSH and LH, as measured by specific immunometric assays, are low. These tumors induce puberty in boys but not in girls, as ovarian production of estrogens cannot take place in the absence of FSH stimulation.

**HEPATIC TUMORS**

All reported cases of hepatoblastoma causing isosexual precocious puberty have been in boys, with the average age of onset of 2 yr (range: 4 mo to 8 yr). An enlarged liver or mass in the right upper quadrant should suggest the diagnosis. Plasma levels of hCG and α-fetoprotein are usually markedly elevated and serve as useful markers for following the effects of therapy. Similarly to other carcinomas of the liver, the prognosis for survival beyond 1-2 yr from the time of diagnosis is poor.

**INTRACRANIAL TUMORS**

Nongerminomatous or mixed germ cell tumors, choriocarcinomas, teratomas, teratocarcinomas, and others account for <5% of intracranial tumors. They are usually located in the neurohypophyseal area or the pineal area and may cause precocious puberty in boys if they secrete hCG, and rarely in girls because of mass effect. Marked elevations of hCG and α-fetoprotein often occur in the cerebrospinal fluid, although elevations in the blood may be modest. Treatment includes radiation, chemotherapy, and debulking surgery.

**TUMORS IN OTHER LOCATIONS**

Very rare locations include the mediastinum, gonads, or even adrenal glands. Mediastinal tumors have been reported to cause precocious puberty in boys with Klinefelter syndrome.

**PERIPHERAL PRECOCIOUS PUBERTY**

The adrenal causes of pseudopuberty are discussed in Chapter 576, and the gonadal causes are discussed in Chapters 584 and 587.

**562.6 McCune-Albright Syndrome (Precocious Puberty with Polyostotic Fibrous Dysplasia and Abnormal Pigmentation)**

Wassim Chemaitilly and Luigi R. Garibaldi

This syndrome of endocrine dysfunction is associated with patchy cutaneous pigmentation and fibrous dysplasia of the skeletal system. It is a rare condition with a prevalence between 1 in 100,000 and 1 in 1,000,000 people. A classical cause of peripheral precocious puberty, it can also induce pituitary, thyroid, and adrenal aberrations. It is characterized by autonomous hyperfunction of many glands and is caused by a missense mutation in the gene encoding the α-subunit of GS, the G protein that stimulates cyclic adenosine monophosphate formation, resulting in the formation of the putative gsp oncogene. Activation of receptors (corticotropin [adrenocorticotropic hormone (ACTH)], TSH, FSH, and LH receptors) that operate via a cyclic adenosine monophosphate–dependent mechanism, as well as cell proliferation, ensue. Because the mutation is somatic rather than genomic, it is expressed differently in different tissues; hence the variability of clinical expression. Precocious puberty has been described predominantly in girls (Fig. 562-4). The average age at onset in affected girls is about 3 yr, but vaginal bleeding has occurred as early as 4 mo of age and secondary sex characteristics have occurred as early as 6 mo. Young girls have suppressed levels of LH and FSH, and there is no response to GnRH or leuprolide stimulation. Estradiol levels vary from normal to markedly elevated (>900 pg/mL), are often cyclic, and may correlate with the size of the recurrent ovarian cysts. In boys, precocious puberty is less common but has been reported in several instances. Unlike ovarian enlargement in girls, testicular enlargement in boys is fairly symmetric. It is followed by the appearance of phallic enlargement and pubic hair, as in normal puberty. Testicular histology has demonstrated large seminiferous tubules and no or minimal Leydig cell hyperplasia; these findings may simply reflect the fact that biopsy specimens were obtained at an early stage of pubertal development. In girls and boys, when the bone age reaches the usual pubertal age range, gonadotropin secretion begins, and the response to GnRH becomes pubertal. Central precocious puberty overrides the antecedent (gonadotropin-independent) precocious pseudopuberty. In girls, menses become more regular, but often not completely so, and fertility has been documented.

Pubertal progression is variable in these patients. Functioning ovarian cysts often disappear spontaneously; aspiration or surgical excision of cysts is rarely indicated, but ovarian torsion may occur.
Familial Incomplete Disorders

Most patients have a demonstrable pituitary tumor. Depot octreotide levels of prolactin are increased in most patients, but fewer than 50% increase during sleep, and are poorly inhibited by oral glucose. Serum of growth even in the absence of precocious puberty. Girls and boys manifested clinically by gigantism or acromegaly or by increased rates adrenalectomy. Suppressed by large doses of dexamethasone. Treatment is bilateral the sexual precocity. ACTH levels are low, and adrenal function is not adrenocortical hyperplasia has occurred in early infancy, antedating ultrasound have been reported. Thyroidectomy is rarely necessary. Iodothyronine levels, suppressed TSH levels, and abnormalities on characteristic of Graves disease. There is an equal distribution between The hyperthyroidism that occurs in this condition differs from that EXTRAGONAL MANIFESTATIONS gonadotropin-dependent mechanism.

For girls with persistent estradiol secretion, agents that interfere with the final step of estrogen biosynthesis (i.e., aromatase inhibitors such as letrozole [1.25-2.5 mg/day orally]) or antiestrogens (such as tamoxifen 5-20 mg/day orally) may limit, to a variable extent, the estrogen effects on pubertal and osseous maturation. The same compounds have also been used in boys, in combination with antiandrogens (such as spironolactone 50-100 mg bid, flutamide 125-250 mg bid, or bicalutamide 25-50 mg daily). These compounds are not approved by the FDA for this indication; tamoxifen, flutamide, and bicalutamide may be hepatotoxic, and high-dose spironolactone may (rarely) cause hyperkalemia. Associated therapy with long-acting analogs of GnRH is indicated only for patients whose puberty has shifted from a gonadotropin-independent to a predominantly gonadotropin-dependent mechanism.

EXTRAGONAL MANIFESTATIONS

The hyperthyroidism that occurs in this condition differs from that characteristic of Graves disease. There is an equal distribution between male and female patients; the goiters are multinodular. Clinical hyperthyroidism is uncommon in children, but goiters, mildly elevated triiodothyronine levels, suppressed TSH levels, and abnormalities on ultrasound have been reported. Thyroidectomy is rarely necessary. In patients with associated Cushing syndrome, bilateral nodular adenocortical hyperplasia has occurred in early infancy, antedating the sexual precocity. ACTH levels are low, and adrenal function is not suppressed by large doses of dexamethasone. Treatment is bilateral adrenalectomy. Increased secretion of growth hormone occurs uncommonly and is manifested clinically by gigantism or acromegaly or by increased rates of growth even in the absence of precocious puberty. Girls and boys are equally affected. Serum levels of growth hormone are elevated, increase during sleep, and are poorly inhibited by oral glucose. Serum levels of prolactin are increased in most patients, but fewer than 50% of the patients have a demonstrable pituitary tumor. Depot octreotide (Sandostatin LAR Depot 10-30 mg IM monthly) or Lanreotide (Somatuline Depot, 60-90 mg SC monthly), long-acting somatostatin analogs, can be used to treat the hypersecretomatropism. The prognosis is favorable for longevity, but deformities, repeated fractures, pain, and occasional cranial nerve compression may result from the bony lesions. Of the extraglandular manifestations, phosphaturia, leading to rickets or osteomalacia, is the most common. Cardiovascular and hepatic involvement is rare but may be life-threatening (severe neonatal cholestasis).

562.7 Familial Male Gonadotropin-Independent Precocious Puberty

Wassim Chemaitilly and Luigi R. Garibaldi

This rare, autosomal dominant form of peripheral precocious puberty is transmitted from affected males and unaffected female carriers of the gene to their male offspring. Signs of puberty appear by 2-3 yr of age. The testes are only slightly enlarged. Testicular biopsies show Leydig cell maturation and, sometimes, marked hyperplasia. Matura-
tion of seminiferous tubules may be present. Testosterone levels are variably and often markedly elevated, even above the adult male range; however, baseline levels of LH are prepubertal, pulsatile secretion of LH is absent, and LH does not respond to stimulation with GnRH or GnRH agonist. The cause for activation of Leydig cells independently of gonadotropin stimulation is a missense mutation of the LH receptor leading to constitutive activation of cyclic adenosine monophosphate production. Osseous maturation may be markedly advanced; when it reaches the pubertal age range, hypothalamic maturation shifts the mechanism of pubertal development to a gonadotropin-dependent one. This sequence of events is similar to that occurring in children with McCune-Albright syndrome (see Chapter 562.6) or in those with congenital adrenal hyperplasia (see Chapter 576.1).

Gonadotropin-independent precocious puberty has been diagnosed in a few unrelated boys with type IA pseudohypoparathyroidism who had a single mutation of the Gα protein. This mutation is inactivating at normal body temperature and causes pseudohypoparathyroidism, but in the cooler temperature of the testes, it is constitutionally activat-
ing, resulting in adenyl cyclase stimulation and production of testos-
terone. Although this mutation differs from the constitutive LH receptor mutation, which usually causes familial male gonadotropin-independent precocious puberty, the end result is the same.

TREATMENT

Young boys have been successfully treated with ketoconazole (600 mg/24 hr in 8 hr divided doses), an antifungal drug that inhibits C-17,20-lyase and testosterone synthesis. Other investigators use a combination of antiandrogens (such as spironolactone 50-100 mg twice a day, flutamide 125–250 mg twice a day, or bicalutamide 25-50 mg daily) and aromatase inhibitors (letrozole 2.5 mg/day, or anastrozole 1 mg/day), because estrogens derived from androgens stimulate bone maturation. These medications are unable to revert the serum testosterone to the normal (prepubertal) concentrations or completely offset the unfavorable effects of the elevated sex hormones. They slow down, but do not halt, the progression of puberty and may not improve the height prognosis. Boys whose GnRH pulse generator has matured require combined therapy with GnRH agonists.

562.8 Incomplete (Partial) Precocious Development

Luigi R. Garibaldi and Wassim Chemaitilly

Isolated manifestations of precocity without development of other signs of puberty are not unusual; development of the breasts in girls and growth of sexual hair in both sexes are the 2 most common forms.
PREMATURE THELARCHE

This term applies to a sporadic, transient condition of isolated breast development that most often appears in the 1st 2 yr of life. In some girls, breast development is present at birth and persists. It may be unilateral or asymmetric and often fluctuates in degree. Growth and osseous maturation are normal or slightly advanced. The genitalia show no evidence of estrogenic stimulation. Breast development may regress after 2 yr, often persists for 3-5 yr, and is rarely progressive. Menarche occurs at the expected age, and reproduction is normal. Basal serum levels of FSH and the FSH response to GnRH stimulation may be greater than that seen in normal controls. Plasma levels of LH and estradiol are consistently less than the limits of detection. Ultrasound examination of the ovaries reveals normal size, but a few small (<9 mm) cysts are not uncommon.

In some girls, breast development may be associated with definite evidence of systemic estrogen effects, such as growth acceleration or bone age advancement. Pelvic sonography may reveal enlarged ovaries or uterus. This condition, referred to as exaggerated or atypical thelarche, differs from central precocious puberty because it spontaneously regresses. Leuprolide or GnRH stimulation elicits a robust FSH response, a low LH response, and (after leuprolide only) a moderate estradiol increment at 24 hr (average: 60-90 pg/mL). The pathogenesis of typical and exaggerated forms of thelarche is unclear. Delayed inactivation of the hypothalamic-pituitary-ovarian axis, which is active during the prenatal and early postnatal period, increased peripheral sensitivity to estrogens, and other possibilities have been proposed, yet are unproven hypotheses. Premature thelarche is a benign condition but may be the first sign of true or peripheral precocious puberty, or it may be caused by exogenous exposure to estrogens. In addition to a detailed history, a bone age should be obtained if there are any unusual features. Random serum concentrations of FSH, LH, and estradiol are generally low and not diagnostic. Pelvic ultrasound examination or leuprolide stimulation testing is rarely indicated. Continued observation is important because the condition cannot be readily distinguished from true precocious puberty. Regression and recurrence suggest functioning follicular cysts. Occurrence of thelarche in children older than 3 yr of age most often is caused by a condition other than benign premature thelarche.

PREMATURE PUBARCHE (ADRENARCHE)

Premature adrenarche has traditionally applied to the appearance of sexual hair before the age of 8 yr in girls or 9 yr in boys without other evidence of maturation. It is much more frequent in girls than in boys. The higher prevalence of this condition in African-American and, to a smaller extent, Latino girls in comparison to white girls may suggest that the cutoff age for the definition of “premature” should be adjusted for different ethnic groups on the basis of epidemiologic data. Hair appears on the mons and labia majora in girls and perineal and scrotal area in boys; axillary hair generally appears later. Adult-type axillary odor is common. Affected children are often slightly advanced in height and osseous maturation. Premature adrenarche is an early maturational event of adrenal androgen production. This event coincides with precocious maturation of the zona reticularis, an associated decrease in 3β-hydroxysteroid dehydrogenase activity, and an increase in C-17,20-lyase activity. These enzymatic changes result in increased basal and ACTH-stimulated serum concentrations of the Δ4-steroids (17-hydroxyprogrenolone and dehydroepiandrosterone) and, to a lesser extent, of the Δ5-steroids (particularly androstenedione) compared with age-matched control subjects. The levels of these steroids and of dehydroepiandrosterone sulfate are usually comparable to those of older children in the early stages of normal puberty. Idiopathic premature adrenarche is a slowly progressive condition that requires no therapy. However, a subset of patients with precocious puberty has 1 or more features of systemic androgen effect, such as marked growth acceleration, clitoral (girls) or phallic (boys) enlargement, cystic acne, or advanced bone age (>2 SD above the mean for age). In these patients with atypical premature adrenarche, an ACTH stimulation test with measurement of steroid intermediates (mainly, serum 17-hydroxyprogesterone concentrations) is indicated to rule out nonclassical congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. Epidemiologic and molecular genetic studies show that the prevalence of nonclassical 21-hydroxylase deficiency is approximately 3-6% of unselected children with precocious pubarche; the prevalence of other enzyme defects (i.e., 3β-hydroxysteroid dehydrogenase or 11β-hydroxylase deficiency) is extremely low. Although idiopathic premature adrenarche has been considered a benign condition, longitudinal observations suggest that approximately 50% of girls with premature adrenarche are at high risk for hyperandrogenism and polycystic ovary syndrome, alone or more often in combination with other components of the so-called metabolic syndrome (insulin resistance possibly progressing to type 2 diabetes mellitus, dyslipidemia, hypertension, increased abdominal fat) as adults. Whether the unfavorable progression to pubertal hyperandrogenism can be prevented by insulin-sensitizing agents (metformin 850-1,000 mg/day) or lifestyle interventions (diet, exercise) remains to be proven in large studies. An increased risk of premature adrenarche and the metabolic syndrome is documented in children born small for their gestational age. This appears to be associated with insulin resistance and decreased β-cell reserve, perhaps as a consequence of fetal undernutrition.

PREMATURE MENARCHE

This is a rare entity, much less frequent than premature thelarche or premature adrenarche, and is a diagnosis of exclusion. In girls with isolated vaginal bleeding in the absence of other secondary sexual characteristics, more common causes, such as vulvovaginitis, a foreign body (typically associated with malodororous discharge), or sexual abuse, and uncommon causes, such as urethral prolapse and sarcoma botryoides, must be carefully excluded. The majority of girls with idiopathic premature menarche have only 1-3 episodes of bleeding: puberty occurs at the usual time, and menstrual cycles are normal. Plasma levels of gonadotropins are low, but estradiol levels may be occasionally elevated, probably owing to episodic ovarian estrogen secretion associated with ovarian follicular cysts that can be detected on ultrasound.

562.9 Medicational Precocity

A variety of medicaments can induce the appearance of secondary sexual characteristics that may be confused with precocious puberty. A careful history focused on exploring the possibility of accidental exposure to, or ingestion of, sex hormones is important. Peripheral precocious puberty has occurred in boys and girls from the accidental ingestion of estrogens (including contraceptive pills) and from the administration of anabolic steroids. The most common cause of medicational precocity is currently related to the widespread use of testosterone gels or creams that are applied to the skin for treatment of male hypogonadism. This has resulted in virilization of children and women following skin contact at, and systemic absorption from, the area where the gel/cream was applied by their family member.

Less commonly, estrogens in cosmetics, hair creams, and breast augmentation creams have caused breast development in girls and gynecomastia in boys, via percutaneous absorption. The high prevalence of premature thelarche and peripheral precocious puberty in Puerto Rico has been attributed to contamination of meats, particularly chicken, with estrogens used in animal husbandry, but has not been proved. Exogenous estrogens may produce a darkening of the areola that is not usually seen in endogenous types of precocity. The precocious changes disappear after cessation of exposure to the hormones.

Bibliography is available at Expert Consult.
Section 2

Disorders of the Thyroid Gland

Chapter 563

Thyroid Development and Physiology

Stephen H. LaFranchi and Stephen A. Huang

FETAL DEVELOPMENT

The fetal thyroid arises from an outpouching of the foregut at the base of the tongue (foramen cecum). It migrates to its normal location over the thyroid cartilage by 8-10 wk of gestation. The thyroid bilobed shape is recognized by 7 wk of gestation, and characteristic thyroid follicle cell and colloid formation is seen by 10 wk. Thyroglobulin synthesis occurs from 4 wk, iodine trapping occurs by 8-10 wk, and thyroxine (T4) and, to a lesser extent, triiodothyronine (T3) synthesis and secretion occur from 12 wk of gestation. There is evidence that several transcription factors—TTF-1/NKX-2.1, TTF-2 (also termed FOXE1), NKX2.5, and PAX8—are important in thyroid gland morphogenesis and differentiation, and possibly also in its caudal migration to its final location. These factors also bind to the promoters of thyroglobulin and thyroid peroxidase genes and so influence thyroid hormone production. Hypothalamic neurons synthesize thyrotropin-releasing hormone (TRH) by 6-8 wk, the pituitary portal vessel system begins development by 8-10 wk, and thyroid-stimulating hormone (TSH) secretion is evident by 12 wk of gestation. Maturation of the hypothalamic-pituitary-thyroid axis occurs over the second half of gestation, but normal feedback relationships are not mature until approximately 3 mo of postnatal life. Other transcription factors, including PROP-1 and Pit-1, are important for differentiation and growth of thyrotrphs, along with somatotrophs and lactotrophs.

THYROID PHYSIOLOGY

The main function of the thyroid gland is to synthesize T3 and T4. The only known physiologic role of iodine (or iodide [I−] in its ionized form) is in the synthesis of these hormones; the recommended dietary allowance of iodine is 30 µg/kg/24 hr for infants, 90-120 µg/24 hr for children, and 150 µg/24 hr for adolescents and adults.

The median iodine intake in the United States decreased by approximately 50% between the 1970s (320 µg/L) and the 1990s (145 µg/L), but it now appears to have stabilized (2009-2010 = 144 µg/L). Whatever the chemical form ingested, iodine eventually reaches the thyroid gland as iodide. Thyroid tissue has an avidity for iodide and is able to trap (with a gradient of 100:1) transport, and concentrate it in the follicular lumen for synthesis of thyroid hormone. Entry of iodide from the circulation into the thyroid is carried out by the sodium–iodide symporter. Iodide diffuses across the cell to the apical membrane where it is transported into the colloid via pendrin.

Before trapped iodide can react with tyrosine, it must be oxidized; this reaction is catalyzed by thyroid peroxidase. Dual oxidase maturation factor 2 (DUOX2) is required to express DUOX2 enzymatic activity, which is required for H2O2 generation, a crucial step in iodide oxidation. The thyroid cells produce thyroglobulin, a large globular glycoprotein with a molecular weight of approximately 660,000, containing approximately 120 tyrosine units. Iodination of tyrosine forms monoiodotyrosine and diiodotyrosine; 2 molecules of diiodotyrosine then couple to form 1 molecule of T4, or 1 molecule of diiodotyrosine and 1 of monoiodotyrosine to form T3. Once formed, hormones are stored as thyroglobulin in the lumen of the follicle (colloid) until ready to be delivered to the body cells. T3 and T4 are liberated from thyroglobulin by activation of proteases and peptidases.

The metabolic potency of T3 is 3-4 times that of T4. In adults, the thyroid produces approximately 100 µg of T4 and 20 µg of T3 daily. Only 20% of circulating T4 is secreted by the thyroid; the remainder is produced by deiodination of T3 in the liver, kidney, and other extrathyroidal tissues by type 1 5′-deiodinase. Selenocysteine is the active center of the iodothyronine deiodinases. Thus, selenium indirectly plays a role in normal growth and development. In the pituitary and brain, approximately 80% of required T3 is produced locally from T4 by a different enzyme, type II 5′-deiodinase. The level of T3 in blood is one fifth of that of T4, but T3 is the physiologically active thyroid hormone.

Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism. Specific thyroid hormone transporters, of which the most important is monocarboxylate transporter 8, facilitate entry of T3 and T4 into cells. Once into the cell, T3 is converted to T4 by type I or II 5′-deiodinase. Intracellular T3 then enters the nucleus, where it binds to thyroid hormone receptors. Thyroid hormone receptors are members of the steroid hormone receptor superfamily that includes glucocorticoids, estrogen, progesterone, vitamin D, and retinoids. Four different isoforms of the thyroid hormone receptor (α, β, γ, and δ) are expressed in different tissues; the protein product of the formerly designated c-erb A protooncogene (THRA2) is the α9 thyroid hormone receptor in the brain and hypothalamus. Thyroid hormone receptors consist of a ligand-binding domain (binds T3, T4, or T3–T4), hinge region, and DNA-binding domain (zinc finger). Binding of T3 activates the thyroid hormone receptor response element, resulting in production of an encoded messenger RNA and protein synthesis specific for the target cell. In this manner, a single hormone, T3, acting through tissue-specific thyroid hormone receptor isoforms and gene-specific thyroid response elements, can produce multiple effects in various tissues.

Approximately 70% of the circulating T3 is firmly bound to T3-binding globulin (TBG). Less-important carriers are T4-binding prealbumin, called prealbumin, and albumin. Only 0.03% of T3 in serum is not bound and comprises free T3. Approximately 50% of circulating T3 is bound to TBG, and 50% is bound to albumin; 0.30% of T3 is unbound, or free, T3. Because the concentration of TBG is altered in many clinical circumstances, its status must be considered when interpreting total T3 or T4 levels.

THYROID REGULATION

The thyroid is regulated by TSH, a glycoprotein produced and secreted by the anterior pituitary. This hormone activates adenylate cyclase in the thyroid gland and is important in all steps of thyroid hormone biosynthesis, from trapping of iodine to release of thyroid hormones. TSH is composed of 2 noncovalently bound subunits (chains): α and β. The α subunit is common to luteinizing hormone, follicle-stimulating hormone, and chorionic gonadotropin; the specificity of each hormone is conferred by the β subunit. TSH synthesis and release are stimulated by TRH, which is synthesized in the hypothalamus and secreted into the pituitary. TRH is found in other parts of the brain besides the hypothalamus and in many other organs; aside from its endocrine function, it may be a neurotransmitter. TRH is a simple tripeptide. In states of decreased production of thyroid hormone, TSH and TRH are increased. Exogenous thyroid hormone or increased thyroid hormone synthesis inhibits TSH and TRH production. Except in the neonate, levels of TRH in serum are very low.

Further control of the level of circulating thyroid hormones occurs in the periphery. In many nonthyroidal illnesses, extrathyroidal production of T4 decreases; factors that inhibit T4 type I 5′-deiodinase include fasting, chronic malnutrition, acute illness, and certain drugs. Such factors increase type III 5′-deiodinase conversion of T4 to reverse T3. Whereas levels of T4 may be significantly decreased, levels of free
T₃ and TSH may remain normal. The decreased levels of T₄ may be a physiologic adaptation, resulting in decreased rates of oxygen production, of substrate use, and of other catabolic processes.

Bibliography is available at Expert Consult.

**563.1 Thyroid Hormone Studies**

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**SERUM THYROID HORMONES**

Methods are available to measure all the thyroid hormones in serum: T₄, free T₄, T₃, and free T₃. A metabolically inert T₃ (3,5′,3′-triiodothyronine), called reverse T₃, is also present in serum. Age must be considered in interpreting results, particularly in the neonate.

Thyroglobulin is a glycoprotein that is secreted through the apical surface of the thyroid follicular cell into the colloid. Small amounts escape into the circulation and are measurable in serum. Levels increase with TSH (also called thyrotropin) stimulation and decrease with TSH suppression. Serum thyroglobulin levels are increased in the neonate, in patients with Graves disease and other forms of autoimmune thyroid disease, and in those with endemic goiter. The most marked elevations of thyroglobulin occur in patients with differentiated carcinoma of the thyroid. Athyreotic infants have markedly reduced levels of thyroglobulin in serum.

Serum TSH levels are the most accurate test of thyroid function. Serum TSH levels are elevated in primary hypothyroidism and suppressed in hyperthyroidism. After the neonatal period, normal levels of TSH are <6 mIU/L. With central (secondary) hypothyroidism, serum TSH may be subnormal, though often it is “inappropriately” in the normal range, despite a low serum T₄ or free T₄ level. TSH appears to be less biologically active in central hypothyroidism. These sensitive (third-generation) TSH assays obviate the need for TRH stimulation in the diagnosis of most patients with thyroid disorders.

**FETAL AND NEWBORN THYROID**

Fetal serum T₄ and free T₄ increase progressively from midgestation to approximately 11.5 µg/dL and 1.5 ng/dL, respectively, at term. Fetal levels of T₃ are low before 20 wk and then gradually increase to approximately 45 ng/dL at term. Reverse T₃ levels (inactive form of T₃), however, are high in the fetus (250 ng/dL at 30 wk) and decrease to 150 ng/dL at term. Serum levels of TSH gradually increase to 10 mU/L at term. Approximately one third of maternal T₄ crosses the placenta to the fetus. Maternal T₄ plays a role in fetal development, especially that of the brain, before the synthesis of fetal thyroid hormone begins. The fetus of a hypothyroid mother may be at risk for neurologic injury, and a hypothyroid fetus may be partially protected by maternal T₄ until delivery. The amount of T₄ that crosses the placenta is not sufficient to interfere with a diagnosis of congenital hypothyroidism in the neonate.

At birth, there is an acute release of TSH; peak serum concentrations reach 60 mU/L 30 min following delivery in full-term infants. A rapid decline occurs in the ensuing 24 hr and a more gradual decline over the next 5 days to <10 mU/L. The acute increase in TSH produces a dramatic increase in levels of T₄ to approximately 16 µg/dL and of T₃ to approximately 300 ng/dL in about 4 hr. This T₄ seems largely derived from increased peripheral conversion of T₄ to T₃. T₃ levels gradually decrease during the 1st 2 wk of life to 12 µg/dL. T₃ levels decline during the 1st wk of life to levels below 200 ng/mL. Serum free T₄ levels are 0.9-2.3 ng/dL in infancy and decline to 0.7-1.8 ng/dL in childhood. Serum free T₃ concentrations are approximately 180-760 pg/dL in infancy and decline to 230-650 pg/dL in childhood. Reverse T₃ levels are maintained for 2 wk (200 ng/dL) and decrease by 4 wk to around 50 ng/dL. In preterm infants, changes in thyroid function after birth are qualitatively similar to but quantitatively smaller than in full-term infants. Serum T₄ and T₃ levels are decreased in proportion to gestational age and birthweight.

**SERUM THYROXINE-BINDING GLOBULIN**

The thyroid hormones are transported in plasma bound to TBG, a glycoprotein synthesized in the liver. Estimation of TBG levels is occasionally necessary because TBG is increased or decreased in a variety of clinical situations, with effects on the level of total T₄ and T₃. TBG binds approximately 70% of T₄ and 50% of T₃. TBG levels increase in pregnancy, in the newborn period, with hepatitis, and with administration of estrogens (oral contraceptives), selective estrogen receptor modulators, heroin or methadone, mitotane, 5-fluorouracil, and perphenazine, and they decrease with androgens, anabolic steroids, glucocorticoids, nicotinic acid, and L-asparaginase. These effects are the results of modulation of hepatic synthesis of TBG. TBG levels may be markedly decreased owing to decreased production with hepatocellular disease or loss in the gut with protein-losing enteropathies or in urine, as in the congenital nephrotic syndrome. Decreased or increased levels of TBG also occur as genetic traits (see Chapter 564).

Some drugs, in particular phenytoin, carbamazepine, furosemide, salicylates, nonsteroidal antiinflammatory drugs, and heparin, also inhibit binding of T₄ and T₃ to TBG. In addition, phenytoin and carbamazepine cause abnormalities of thyroid function tests by another mechanism. They stimulate hepatic cytochrome P450 degradation of T₄ and accelerate transport of T₄ into tissues.

**IN VIVO RADIONUCLIDE STUDIES**

Markedly improved direct tests of thyroid hormone have made radioactive iodine uptake studies less necessary. The iodine trapping or concentrating mechanism of the thyroid can be evaluated by measuring the uptake of radioactive isotope ¹²³I (half-life: 13 hr). The technology allows doses of radioiodine (0.1-0.5 mCi) that are only a fraction of those used with ¹³¹I. Technetium (⁹⁹mTc) is a particularly useful radioisotope for children because in contrast to iodine, it is trapped but not organified by the thyroid and has a half-life of only 6 hr. Thyroid scanning may be indicated to assess the presence of thyroid tissue in questions of thyroid dysgenesis and to detect ectopic thyroid tissue, and thyroid uptake may be indicated to evaluate possible “hot” thyroid nodules. Diagnostic studies should be performed with ⁹⁹mTc pertechnetate or ¹²³I because they have the advantages of lower radiation exposure and high-quality scintigrams. Radioiodine treatment, which may be used to treat children with Graves hyperthyroidism or differentiated thyroid cancer, employs administration of ¹³¹I, which has a longer half-life (8 days) and greater killing effect.

**THYROID ULTRASONOGRAPHIC STUDIES**

Thyroid ultrasound examinations can determine the location, size, and shape of the thyroid gland, and they are useful for assessing the solid or cystic nature of nodules. Ultrasound is not as reliable as radionuclide studies in evaluating infants with suspected thyroid dysgenesis, particularly ectopic glands. Ultrasound examinations are useful in identifying normal thyroid gland position in children with suspected thyroglossal duct cysts. In children with autoimmune thyroiditis, ultrasound reveals scattered hypoechoogenicity. Ultrasound examinations are more accurate than physical examination in estimating goiter size and assessing thyroid nodules. Certain characteristics of thyroid nodules, such as blurred margins, microlcalfications, hypoechogeticity, taller-than-wide shape, capsular extension, and increased vascularity, increase the likelihood of thyroid cancer, although none of these features is 100% sensitive or specific.

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Kopp P: Thyroid hormone synthesis. In Braverman LE, Cooper DS, editors: *Werner & Ingbar’s the thyroid: a fundamental and clinical text*, ed 10, Philadelphia, 2013, Lippincott Williams & Wilkins, pp 48–73.
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Abnormalities in levels of thyroxine-binding globulin (TBG) are not associated with clinical disease and do not require treatment. They are usually uncovered by a chance finding of abnormally low or high levels of thyroxine (T₄) and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

TBG deficiency occurs as an X-linked dominant disorder. Congenital TBG deficiency is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T₄ as the primary screening test. Affected patients have low levels of total T₄ and elevated resin triiodothyronine uptake, but levels of free T₄ and thyroid-stimulating hormone are normal. The diagnosis is confirmed by the finding of absent or low levels of TBG. TBG deficiency occurs in 1 in 2,400 male newborns, 36% of whom have TBG levels <1 mg/dL. Milder forms of TBG deficiency occur in approximately 1 in 42,000 heterozygous female newborns. Complete TBG deficiency (<5 µg/dL) occurs much less often. To date, more than 25 different mutations have been reported in the TBG gene, resulting in either decreased TBG levels or reduced affinity of TBG for T₄. Table 564-1 lists causes of acquired TBG deficiency.

TBG excess also is a harmless X-linked dominant anomaly, occurring in approximately 1 in 25,000 persons. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T₄ is elevated, triiodothyronine is variably elevated, thyroid-stimulating hormone and free T₄ are normal, and resin triiodothyronine uptake is decreased. The elevated levels of TBG confirm the diagnosis. In affected neonates, levels of T₄ as high as 95 µg/dL have been found, which decrease to 20-30 µg/dL after 2-3 wk. Such high levels of T₄ may be related in part to the normally elevated levels of TBG in neonates, presumably as an effect of maternal estrogens. Affected patients are euthyroid. Family studies may be indicated to alert other affected family members. Table 564-1 lists causes of acquired TBG excess.

**Familial dysalbuminemic hyperthyroxinemia** is an autosomal dominant disorder that may be confused with hyperthyroidism. Markedly increased binding of T₄ to an abnormal albumin variant leads to increased serum concentrations of T₄. However, the levels of free T₃, free triiodothyronine, and thyroid-stimulating hormone are normal.

**Table 564-1** Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

<table>
<thead>
<tr>
<th>DECREASED TBG</th>
<th>INCREASED TBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Selective estrogen receptor modulators</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Hepatocellular disease</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Severe illness</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Protein-losing nephropathies</td>
<td>Heroin, methadone</td>
</tr>
<tr>
<td>Protein-losing enteropathies</td>
<td>Mitotane</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>5-Flourouracil</td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>Perphenazine</td>
</tr>
</tbody>
</table>

Levels of triiodothyronine are normal or only slightly elevated. Affected patients are euthyroid.

*Bibliography is available at Expert Consult.*
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Benvena S: Thyroid hormone transport proteins and the physiology of hormone binding. In Braverman LE, Cooper DS, editors: Werner & Ingbar's the thyroid: a fundamental and clinical text, ed 10, Philadelphia, 2013, Lippincott Williams & Wilkins, pp 93–102.


Hypothyroidism results from deficient production of thyroid hormone, either from a defect in the gland itself (primary hypothyroidism) or a result of reduced thyroid-stimulating hormone (TSH) stimulation (central or hypopituitary hypothyroidism; Table 565-1). The disorder may be manifested from birth (congenital) or acquired. When symptoms appear after a period of apparently normal thyroid function, the disorder may be truly acquired or might only appear so as a result of one of a variety of congenital defects in which the manifestation of the deficiency is delayed.

**CONGENITAL HYPOTHYROIDISM**

Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis. Some cases are familial; these are usually caused by one of the inborn errors of thyroid hormone synthesis (dys-hormonogenesis) and may be associated with a goiter. Most infants with congenital hypothyroidism are detected by newborn screening programs in the 1st few wk after birth, before obvious clinical symptoms and signs develop. In infants born in areas with no screening program, severe cases manifest features in the 1st few wk of life, but in cases of milder deficiency, manifestations may be delayed for months.

**Epidemiology**

The prevalence of congenital hypothyroidism based on nationwide programs for neonatal screening was initially reported at 1 in 4,000 infants worldwide. Over the last 2 decades, the prevalence has dropped to 1 in 2,000, likely the result of detection of milder cases of hypothyroidism. Studies from the United States report that the prevalence is lower in black Americans and higher in Asian-Americans and Pacific Islanders, Hispanics, and Native Americans as compared to white babies.

**Etiology**

See Table 565-1.

**Primary Hypothyroidism**

**Thyroid Dysgenesis.** Some form of thyroid dysgenesis (aplasia, hypoplasia, or an ectopic gland) is the most common cause of permanent congenital hypothyroidism, accounting for 80-85% of cases. In approximately 33% of cases of dysgenesis, even sensitive radionuclide scans can find no remnants of thyroid tissue (aplasia). In the other 66% of infants, rudiments of thyroid tissue are found in an ectopic location, anywhere from the base of the tongue (lingual thyroid) to the normal position in the neck (hypoplasia). Thyroid dysgenesis has a 2:1 female: male ratio.

The cause of thyroid dysgenesis is unknown in most cases. Thyroid dysgenesis occurs sporadically, but familial cases occasionally have been reported. The finding that thyroid developmental anomalies, such as thyroglossal duct cysts and hemiagenesis, are present in 8-10% of 1st-degree relatives of infants with thyroid dysgenesis supports an underlying genetic component.

Mutations in several transcription factors important for thyroid morphogenesis and differentiation (including TTF-1/NKX2.1, TTF-2 [also termed FOXE1], and PAX8) are monogenic causes of approximately 2% of the cases of thyroid dysgenesis. In addition, genetic
defects leading to absent or ineffective thyrotropin (TSH) receptor binding or signaling have been described.

The transcription factor TTF-1/NKX2.1 is expressed in the thyroid, lung, and central nervous system. Mutations in TTF-1/NKX2.1 are reported to result in congenital hypothyroidism, respiratory distress, and persistent neurologic problems, including chorea and ataxia, despite early thyroid hormone treatment. NKX2.5 is expressed in the thyroid and heart. Mutations in NKX2.5 are associated with congenital hypothyroidism and cardiac malformations. PAX-8 is expressed in the thyroid and kidney. Mutations in PAX-8 are associated with congenital hypothyroidism and kidney and ureteral malformations.

The common finding of thyroid dysgenesis confined to only 1 of a pair of monozygotic twins suggests the operation of a deleterious factor during intrauterine life. Maternal antithyroid antibodies might be that factor. Although thyroid peroxidase antibodies have been detected in some mother–infant pairs, there is little evidence of their pathogenicity. The demonstration of thyroid growth-blocking and cytotoxic antibodies in some infants with thyroid dysgenesis, as well as in their mothers, suggests a more likely pathogenetic mechanism.

**Defective Synthesis of Thyroxine (Dys hormonogenesis).** A variety of defects in the biosynthesis of thyroid hormone can result in congenital hypothyroidism; these account for 15% of cases detected by neonatal screening programs (1 in 30,000–50,000 live births). These defects are transmitted in an autosomal recessive manner. A goiter is almost always present. When the defect is incomplete, compensation occurs, and onset of hypothyroidism may be delayed for years.

**Defect of Iodide Transport.** Defect of iodide transport is rare and involves mutations in the sodium–iodide symporter. Among the several cases now reported, it has been found in 9 related infants of the Hutterite sect, and approximately 50% of the cases are from Japan. Consanguinity is a factor in approximately 30% of the families.

In the past, clinical hypothyroidism, with or without a goiter, often developed in the 1st few months of life; the condition has been detected in neonatal screening programs. In Japan, however, untreated patients acquire goiter and hypothyroidism after 10 yr of age, perhaps because of the very high iodine content (often 19 mg/24 hr) of the Japanese diet.

The energy-dependent mechanisms for concentrating iodide are defective in the thyroid and salivary glands. In contrast to other defects of thyroid hormone synthesis, uptake of radioiodine and pertechnetate is low; a reduced saliva:serum ratio of 1.2-1 will support the diagnosis, confirmed by finding a mutation in the sodium–iodide symporter gene. This condition responds to treatment with large doses of potassium iodide, but treatment with l-thyroxine is preferable.

**Thyroid Peroxidase Defects of Organification and Coupling.** Thyroid peroxidase defects of organification and coupling are the most common of the thyroxine (T₄) synthetic defects. After iodide is trapped by the thyroid, it is rapidly oxidized to reactive iodine, which is then incorporated into tyrosine units on thyroglobulin. This process requires generation of H₂O₂. Thyroid peroxidase, and hematin (an enzyme cofactor); defects can involve each of these components, and there is considerable clinical and biochemical heterogeneity. In the Dutch neonatal screening program, 23 infants were found with a complete organification defect (1 in 60,000 live births), but its prevalence in other areas is unknown. A characteristic finding in all patients with this defect is a marked “discharge” of thyroid radioactivity when perchlorate or thiocyanate is administered 2 hr after administration of a test dose of radioiodine. In these patients, perchlorate discharges 40-90% of radioiodine compared with <10% in normal persons. Several mutations in the thyroid peroxidase gene have been reported in children with congenital hypothyroidism.

**Dual oxidase maturation factor 2 (DUOX2)** is required to express DUOX2 enzymatic activity, which is required for H₂O₂ generation, a crucial step in iodide oxidation. Biallelic DUOX2 mutations produce permanent congenital hypothyroidism, whereas monoallelic mutations are associated with transient hypothyroidism. DUOX2 mutations can also cause permanent or transient congenital hypothyroidism. DUOX2 mutations are relatively common, present in 30% of cases of apparent dys hormonogenesis, whereas DUOX2 mutations are relatively rare, present in 2% of such cases.

**Pendred syndrome** is an autosomal recessive disorder caused by a mutation in the chloride–iodide transport protein common to the thyroid gland and the cochlea. Pendred syndrome is comprised of sensorineural deafness and goiter; it is the most common cause of syndromic deafness. Pendrin allows transport of iodide from the follicular cell into the colloid where it undergoes organification to iodine and incorporation into the tyrosine residues on thyroglobulin. Patients with a mutation in the pendrin gene have impaired iodide organification and a positive perchlorate discharge.

**Defects of Thyroglobulin Synthesis.** Defects of thyroglobulin synthesis are a heterogeneous group of disorders characterized by goiter, elevated serum TSH, low T₄ levels, and absent or low levels of thyroglobulin. It has been reported in approximately 100 patients. Molecular defects, primarily point mutations, have been described in several patients.

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**Table 565-1** Etiologic Classification of Congenital Hypothyroidism

<table>
<thead>
<tr>
<th>PRIMARY HYPOTHYROIDISM</th>
<th>Etiologic Classification of Congenital Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect of fetal thyroid development (dysgenesis)</td>
<td>• Aplasia</td>
</tr>
<tr>
<td>• Hypoplasia</td>
<td>• Ectopia</td>
</tr>
<tr>
<td>Defect in thyroid hormone synthesis (dys hormonogenesis)</td>
<td>• Iodide transport defect from blood into follicular cell: mutation in thyroid hormone genes</td>
</tr>
<tr>
<td>• Defective iodide transport from follicular cell into colloid: mutation in Pendrin transport protein</td>
<td>• Thyroid organification, or coupling defect: mutation in thyroid peroxidase gene</td>
</tr>
<tr>
<td>• Thyroid hormone unresponsiveness</td>
<td>• Defects in H₂O₂ generation: mutations in DUOX2 maturation factor or DUOX2 gene</td>
</tr>
<tr>
<td>• Maternal antibodies: thyrotropin receptor–blocking antibody</td>
<td>• Thyroglobulin synthesis defect: mutation in thyroglobulin gene</td>
</tr>
<tr>
<td>• Deiodination defect: mutation in DEHALI gene</td>
<td>• Thyroid hormone unresponsiveness</td>
</tr>
<tr>
<td>• Mutation in TSH receptor</td>
<td>• Maternal antibodies: thyrotropin receptor–blocking antibody</td>
</tr>
<tr>
<td>• Defective TSH signaling: Gα mutation (e.g., type IA pseudohypoparathyroidism)</td>
<td>• Resistance to thyroid hormone</td>
</tr>
<tr>
<td>Defect in thyroid hormone transport: mutation in monocarboxylate transporter 8 (MCT8) gene</td>
<td>Maternal medications: thyrotropin receptor–blocking antibody (TRBAb, measured as thyrotropin-binding inhibitor immunoglobulin)</td>
</tr>
<tr>
<td>Iodine deficiency (endemic goiter)</td>
<td>Iodine deficiency (endemic goiter)</td>
</tr>
<tr>
<td>Maternal medications</td>
<td>Maternal medications</td>
</tr>
<tr>
<td>• Iodides, amiodarone</td>
<td>• Propylthiouracil, methimazole</td>
</tr>
<tr>
<td>• Propylthiouracil, methimazole</td>
<td>• Radiodiode</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone.
Defects in Deiodination. Monoiodotyrosine and diiodotyrosine released from thyroglobulin are normally deiodinated within the thyroid or in peripheral tissues by a deiodinase. The liberated iodine is recycled in the synthesis of thyroid hormones. The DEHAL1 gene encodes iodotyrosine deiodinase in the thyroid. DEHAL1 mutations are relatively rare; patients with deiodinase deficiency experience severe iodine loss from the constant urinary excretion of nondeiodinated tyrosines, leading to hormonal deficiency and goiter. The deiodination defect may be limited to thyroid tissue only or to peripheral tissue only, or it may be universal.

Thyrotropin Hormone Unresponsiveness. A mutation in the TSH receptor gene is a relatively uncommon autosomal recessive cause of congenital hypothyroidism. Both homozygous and compound heterozygous mutations in the TSH receptor gene have been reported. Infants with a severe defect have elevated TSH levels and will be detected by newborn screening, whereas other patients with a mild defect remain euthyroid without treatment. A study of infants with congenital hypothyroidism detected by newborn screening from Tokyo reported TSH receptor mutations in 4.3% of patients (1 in 118,000 live births), with a founder mutation (p.R450H) accounting for 70% of gene defects.

Mild congenital hypothyroidism has been detected in newborn infants who subsequently proved to have type 1 pseudohyoparathyroidism. The molecular cause of resistance to TSH in these patients is the generalized impairment of cyclic adenosine monophosphate activation caused by genetic defect of the α subunit of the guanine nucleotide regulatory protein Gs (see Chapter 572).

Defects in Thyroid Hormone Transport. Passage of thyroid hormone into the cell is facilitated by plasma membrane transporters. A mutation in one such transporter gene, monocarboxylate transporter 8 (MCT8), located on the X chromosome (Allan-Herndon-Dudley syndrome), has now been reported in multiple patients. The defective transporter impairs passage of T3 and triiodothyronine (T3) into cells; this syndrome is characterized by elevated serum TSH levels, low T4 levels, and normal or mildly elevated TSH levels. Neurologic manifestations include severe developmental delay, reduced muscle mass, initial hypotonia that evolves into spastic paraplegia, dystarthria, and athetoid movements.

Resistance to Thyroid Hormone

This autosomal dominant disorder is caused by mutations in the thyroid hormone receptor. Most patients have a goiter, and levels of T4, T3, free T4, and free T3 are elevated. These findings often have led to the erroneous diagnosis of Graves disease, although most affected patients are clinically euthyroid. The unresponsiveness can vary among tissues. There may be subtle clinical features of hypothyroidism, including developmental delay, growth retardation, and delayed skeletal maturation. On the other hand, there may be clinical features compatible with hyperthyroidism, such as tachycardia and hyperreflexia. It is presumed that these patients have varying tissue resistance to thyroid hormone. One neurologic manifestation is an increased association of attention-deficit/hyperactivity disorder; the converse is not true because patients with attention-deficit/hyperactivity disorder do not have an increased risk of thyroid hormone resistance.

TSH levels are diagnostic in that they are not suppressed as in Graves disease but instead are moderately elevated or normal but inappropriate for the levels of T3 and T4. The failure of TSH suppression indicates that the resistance is generalized and affects the pituitary gland as well as peripheral tissues. More than 40 distinct point mutations in the hormone-binding domain of the β-thyroid receptor are identified. Different phenotypes do not correlate with genotypes. The same mutation has been observed in patients with generalized or isolated pituitary resistance, even in different members of the same family. A child homozygous for the receptor mutation showed unusually severe resistance. These cases support the dominant negative effect of mutant receptors, in which the mutant receptor protein inhibits normal receptor action in heterozygotes. Elevated levels of T3 on neonatal thyroid screening should suggest the possibility of this diagnosis. No treatment is usually required unless growth and skeletal retardation are present.

Two infants of consanguineous matings are known to have an autosomal recessive form of thyroid resistance. These infants had manifestations of hypothyroidism early in life, and genetic studies revealed a major deletion of the β-thyroid receptor in 1 of them. The resistance appears to be more severe in this form of the entity.

Some patients have greater resistance to thyroid hormone in the pituitary gland as compared to peripheral tissues. Because the peripheral tissues are not resistant to thyroid hormones, the patient has a goiter and manifestations of hyperthyroidism. The laboratory findings are the same as those seen with generalized thyroid hormone resistance. This condition must be differentiated from a pituitary TSH-secreting tumor. Different treatments, including d-thyroxine, triiodothyroacetic acid, and tetraiodothyroacetic acid, have been successful in some patients. Bromocriptine administration, which interferes with TSH secretion, was reported to be successful in another patient. Whether isolated pituitary resistance to thyroid hormone exists as a distinct entity is controversial; it may be a variant of generalized resistance to thyroid hormone with varying tissue responsiveness.

Although the majority of patients with resistance have mutations in the thyroid hormone receptor β gene, a child with a mutation in the thyroid hormone receptor α gene has been reported. This patient presented at age 6 yr with growth retardation, delayed development, and constipation. Genetic analysis showed a heterozygous nonsense mutation in the thyroid hormone receptor α gene that, like β gene mutations, inhibited wild-type receptor action in a dominant negative manner.

Thyrotropin Receptor-Blocking Antibody. Maternal TSH receptor-blocking antibody (TRBAb) is an unusual cause of transitory congenital hypothyroidism. Transplacental passage of maternal TRBAb inhibits binding of TSH to its receptor in the neonate. Maternal TRBAb accounts for 2% of cases detected by neonatal screening programs (1 in 50,000-100,000 infants). It should be suspected whenever there is a history of maternal autoimmune thyroid disease, including Hashimoto thyroiditis or Graves disease, maternal hypothyroidism on replacement therapy, or recurrent congenital hypothyroidism of a transient nature in previous siblings. In these situations, maternal levels of TRBAb (measured as thyrotropin-binding inhibitor immunoglobulin) should be determined during pregnancy. Affected infants and their mothers also can have thyrotropin receptor-stimulating antibodies and thyroid peroxidase antibodies. Technetium pertechnetate and 123I scans might fail to detect any thyroid tissue, mimicking thyroid agenesis, but ultrasonography will show a thyroid gland. After the condition remits, a normal thyroid gland is demonstrable by scanning following discontinuation of replacement therapy. The half-life of the antibody is 21 days, and remission of the hypothyroidism occurs in approximately 3-6 mo. Correct diagnosis of this cause of congenital hypothyroidism prevents unnecessary protracted treatment, alerts the clinician to possible recurrences in future pregnancies, and allows a favorable prognosis.

Radioiodine Administration. Hypothyroidism can occur as a result of inadvertent administration of radioiodine during pregnancy for treatment of Graves disease or cancer of the thyroid. The fetal thyroid is capable of trapping iodide by 70-75 days of gestation. Whenever radioiodine is administered to a woman of childbearing age, a pregnancy test must be performed before a therapeutic dose of 131I is given, regardless of the menstrual history or putative history of contraception. Administration of radioactive iodine to lactating women is also contraindicated because it is readily excreted in milk.

Iodine Exposure. Congenital hypothyroidism can result from fetal exposure to excessive iodides. Perinatal exposure can occur with the use of iodine antiseptic to prepare the skin for cesarean section or painting of the cervix before delivery. It has also been reported in infants born to mothers who consumed large amounts of iodine daily (up to 12 mg) in the form of nutritional supplements and in mothers in Japan who consumed large quantities of iodine-rich seaweed. These conditions are transitory and must not be mistaken for the other forms of hypothyroidism. In the neonate, topical iodine-containing antiseptics used in nurseries and by surgeons can also cause transient congenital hypothyroidism, especially in low-birthweight infants, and can
lead to abnormal results on neonatal screening tests. In older children, the usual sources of iodides are proprietary preparations used to treat asthma. In a few instances, the cause of hypothyroidism was amiodarone, an antiarrhythmic drug with high iodine content. In most of these instances, goiter is present (see Chapter 567).

Iodine-Deficiency Endemic Goiter. See Chapter 567.3.

Iodine deficiency or endemic goiter is the most common cause of congenital hypothyroidism worldwide. The recommended intake of iodine in adults is 150 µg daily, increasing to 250 µg daily during pregnancy to allow for fetal iodine requirements. Despite efforts at universal iodization of salt in many countries, economic, political, and practical obstacles make achieving this objective difficult. While the U.S. population is iodine-sufficient as a whole, approximately 15% of women of reproductive age fall into the iodine-deficient category. Borderline iodine deficiency is more likely to cause problems in preterm infants who depend on a maternal source of iodine for normal thyroid hormone production.

Central (Hypopituitary) Hypothyroidism

Thyrotropin and Thyrotropin-Releasing Hormone Deficiency. Deficiency of TSH and central hypothyroidism can occur in any of the conditions associated with developmental defects of the pituitary or hypothalamus (see Chapter 557). More often in these conditions, the deficiency of TSH is secondary to a deficiency of thyrotropin-releasing hormone (TRH). TSH-deficient hypothyroidism is found in 1 in 30,000-50,000 infants; most screening programs are designed to detect primary hypothyroidism, so most of these cases are not detected by neonatal thyroid screening. The majority of affected infants have multiple pituitary deficiencies and present with hypoglycemia, persistent jaundice, and micrognathia in association with septooptic dysplasia, midline cleft lip, midface hypoplasia, and other midline facial anomalies.

Mutations in genes coding for transcription factors essential to pituitary development, cell type differentiation, and hormone synthesis are associated with congenital TSH deficiency. PIT-1 mutations include TSH deficiency associated with growth hormone and prolactin deficiency. Patients with PROP-1 mutations (“prophet of pit-1”) have not only TSH, growth hormone, and prolactin deficiency but also luteinizing hormone and follicle-stimulating hormone deficiency and variable adrenocorticotrophic hormone deficiency. HESX1 mutations are associated with TSH, growth hormone, prolactin, and adrenocorticotrophic hormone deficiencies and are found in some patients with optic nerve hypoplasia (septooptic dysplasia syndrome; see Chapter 591).

Isolated deficiency of TSH is a rare autosomal recessive disorder that has been reported in several sibships. DNA studies in affected families members reveal defects in the TSH β-subunit gene, including point mutations, frame shifts causing a stop codon, and splice-site mutations. Depending on the specific mutation, serum TSH levels may be undetectable, measureable, or elevated. The diagnosis is usually delayed because the serum TSH level is not elevated in most cases, and such patients are not detected by newborn screening programs.

Thyrotropin-Releasing Hormone Receptor Abnormality. Mutations in the TRH receptor gene, a rare cause of congenital central hypothyroidism, have now been reported in a few families. This condition, which results in isolated TSH deficiency and hypothyroidism, was suspected because of failure of both TSH and prolactin to respond to TRH stimulation.

Thyroid Function in Preterm Babies

Postnatal thyroid function in preterm babies is qualitatively similar but quantitatively reduced compared with that of term infants. The cord serum T4 is decreased in proportion to gestational age and birthweight. The postnatal TSH surge is reduced, and the more premature, very-low-birthweight infants with complications of prematurity, such as respiratory distress syndrome, actually experience a decrease in serum T4 in the 1st wk of life. As these complications resolve, the serum T4 gradually increases so that generally by 6 wk of life it enters the T4 range seen in term infants. Serum free T4 concentrations seem less affected, and when measured by equilibrium dialysis, these levels are often normal. Preterm babies also have a higher incidence of “delayed” TSH elevation and apparent transient primary hypothyroidism. Premature infants of <28 wk of gestation might have problems resulting from a combination of immaturity of the hypothalamic-pituitary-thyroid axis and loss of the maternal contribution of thyroid hormone and so may be candidates for temporary thyroid hormone replacement; further studies are needed.

Clinical Manifestations

Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This situation is attributed to partial transplacental passage of maternal T4, which provides fetal levels that are approximately 33% of normal at birth. Despite this maternal contribution of T4, hypothyroid infants still have a low serum T4 and elevated TSH level and so will be identified by newborn screening programs.

The clinician depends on neonatal screening tests for the diagnosis of congenital hypothyroidism. Some babies escape newborn screening, and laboratory errors occur, so awareness of early symptoms and signs must be maintained. Congenital hypothyroidism caused by thyroid dysgenesis, the most common etiology, is twice as common in girls as in boys. Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn because the signs and symptoms are usually not sufficiently developed. It can be suspected and the diagnosis established during the early weeks of life if the initial, but less characteristic, manifestations are recognized. Birthweight and length are normal, but head size may be slightly increased because of myxedema of the brain. The anterior and posterior fontanels are open widely; observation of this sign at birth can serve as an initial clue to the early recognition of congenital hypothyroidism. Only 3% of normal newborn infants have a posterior fontanel larger than 0.5 cm. Prolongation of physiologic jaundice, caused by delayed maturation of glucuronide conjugation, may be the earliest sign. Feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking spells during nursing, are often present during the 1st mo of life. Respiratory difficulties, partly caused by the large tongue, include apnea episodes, noisy respirations, and nasal obstruction. Some infants may develop respiratory distress syndrome. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. There may be constipation that does not usually respond to treatment. The abdomen is large, and an umbilical hernia is usually present. The temperature is subnormal, often <35°C (95°F), and the skin, particularly that of the extremities, may be cold and mottled. Edema of the genitals and extremities may be present. The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common. Macrocytic anemia is often present and is refractory to treatment with hematins. Because symptoms appear gradually, the clinical diagnosis is often delayed.

Approximately 10% of infants with congenital hypothyroidism have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported. Infants with congenital hypothyroidism may have associated hearing loss. As noted under “Etiology” above, specific mutations in genes involved in thyroid gland development result in “syndromic” congenital hypothyroidism. Mutations in NKK2.1 (TTF-1), present in the thyroid gland, lungs, and brain, are characterized by congenital hypothyroidism, respiratory distress syndrome, and ataxia, or even choreoathetosis. Mutations in NKK2.5 result in congenital hypothyroidism and associated congenital heart defects. Mutations in TTF-2, present in the thyroid gland, palate, and hair, include congenital hypothyroidism, cleft palate, and spiky hair. Mutations in PAX-8, present in the thyroid gland and kidneys, present with congenital hypothyroidism and genitourinary anomalies, including renal agenesis.

If congenital hypothyroidism goes undetected and untreated, these manifestations progress. Retardation of physical and mental development becomes greater during the following months, and by 3–6 mo of age the clinical picture is fully developed (Fig. 565-1). When there is only partial deficiency of thyroid hormone, the symptoms may be milder, the syndrome incomplete, and the onset delayed. Although breast milk contains significant amounts of thyroid hormones,
Affected children come to clinical attention because of a growing mass hormone for many years, or it eventually fails in early childhood. (lingual, sublingual, subhyoid) produce adequate amounts of thyroid levels of thyroglobulin are usually low in infants with thyroid agenesis at the base of the tongue or in the midline of the neck, usually at the level of the hyoid. Occasionally, ectopia is associated with thyroglossal duct cysts. It can occur in siblings. Surgical removal of ectopic thyroid tissue from a euthyroid patient usually results in hypothyroidism, because most such patients have no other thyroid tissue.

Laboratory Findings
In developed countries, infants with congenital hypothyroidism are identified by newborn screening programs. Blood obtained by heel-prick between 2 and 5 days of life is placed on a filter paper card and sent to a central screening laboratory. The early approach to newborn screening in North America and Europe began with measure of levels of T4, followed by measurement of TSH when T4 is low. This approach identifies infants with primary hypothyroidism, some with central or hypopituitary hypothyroidism, and infants with a delayed elevation in TSH levels. Over time, many neonatal screening programs in North America, Europe, and elsewhere in the world have switched to an initial TSH measurement. This approach will detect infants with primary hypothyroidism and infants with milder, subclinical hypothyroidism (normal T4, elevated TSH), but it may not detect infants with delayed TSH elevation or with central or hypopituitary hypothyroidism. With any of these tests, special care should be given to the normal range of values for age of the patient, particularly in the first weeks of life (Table 565-2). Regardless of the approach used for screening, some infants escape detection because of technical or human errors; clinicians must maintain their vigilance for clinical manifestations of hypothyroidism.

Serum levels of T4 or free T4 are low; serum levels of T3 may be normal and are not helpful in the diagnosis. If the defect is primarily in the thyroid, levels of TSH are elevated, often to >100 mU/L. Serum levels of thyroglobulin are usually low in infants with thyroid agenesis or defects of thyroglobulin synthesis or secretion, whereas they are elevated with ectopic glands and other inborn errors of T4 synthesis, but there is a wide overlap of ranges.

Special attention should be paid to identical twins; in several reported cases, neonatal screening failed to detect the affected twin with hypothyroidism, and the diagnosis was not made until the infants were 4-5 mo of age. In these cases, transfusion of euthyroid blood from the unaffected twin normalized the serum levels of T4 and TSH in the...
affected twin at the initial screening. Many newborn screening pro-
grams perform a routine second test in same-sex twins.

Retardation of osseous development can be shown radiographi-
cally at birth in approximately 60% of congenitally hypothyroid infants
and indicates some deprivation of thyroid hormone during intrauter-
ine life. The distal femoral and proximal tibial epiphyses, normally
present at birth, are often absent (Fig. 565-2A). In undetected and
untreated patients, the discrepancy between chronologic age and
osseous development increases. The epiphyses often have multiple
foci of ossification (epiphyseal dysgenesis; Fig. 565-2B); deformity

---

**Table 565-2** Thyroid Function Tests

<table>
<thead>
<tr>
<th>AGE</th>
<th>U.S. REFERENCE VALUE</th>
<th>CONVERSION FACTOR</th>
<th>SI REFERENCE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THYROID THYROGLOBULIN, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>14.7-101.1 ng/mL</td>
<td>×1</td>
<td>14.7-101.1 µg/L</td>
</tr>
<tr>
<td>Birth to 35 mo</td>
<td>10.6-92.0 ng/mL</td>
<td>×1</td>
<td>10.6-92.0 µg/L</td>
</tr>
<tr>
<td>3-11 yr</td>
<td>5.6-41.9 ng/mL</td>
<td>×1</td>
<td>5.6-41.9 µg/L</td>
</tr>
<tr>
<td>12-17 yr</td>
<td>2.7-21.9 ng/mL</td>
<td>×1</td>
<td>2.7-21.9 µg/L</td>
</tr>
<tr>
<td><strong>THYROID-STIMULATING HORMONE, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature Infants (28-36 wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st wk of life</td>
<td>0.7-27.0 mIU/L</td>
<td>×1</td>
<td>0.7-27.0 mIU/L</td>
</tr>
<tr>
<td>Term Infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth to 4 days</td>
<td>1.0-17.6 mIU/L</td>
<td>×1</td>
<td>1.0-17.6 mIU/L</td>
</tr>
<tr>
<td>2-20 wk</td>
<td>0.6-5.6 mIU/L</td>
<td>×1</td>
<td>0.6-5.6 mIU/L</td>
</tr>
<tr>
<td>5 mo-20 yr</td>
<td>0.5-5.5 mIU/L</td>
<td>×1</td>
<td>0.5-5.5 mIU/L</td>
</tr>
<tr>
<td><strong>THYROXINE-BINDING GLOBULIN, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>1.4-9.4 mg/dL</td>
<td>×10</td>
<td>14.94 mg/L</td>
</tr>
<tr>
<td>1-4 wk</td>
<td>1.0-9.0 mg/dL</td>
<td>×10</td>
<td>10.90 mg/L</td>
</tr>
<tr>
<td>1-12 mo</td>
<td>2.0-7.6 mg/dL</td>
<td>×10</td>
<td>20.76 mg/L</td>
</tr>
<tr>
<td>1-5 yr</td>
<td>2.9-5.4 mg/dL</td>
<td>×10</td>
<td>29.54 mg/L</td>
</tr>
<tr>
<td>5-10 yr</td>
<td>2.5-5.0 mg/dL</td>
<td>×10</td>
<td>25.50 mg/L</td>
</tr>
<tr>
<td>10-15 yr</td>
<td>2.1-4.6 mg/dL</td>
<td>×10</td>
<td>21.46 mg/L</td>
</tr>
<tr>
<td>Adult</td>
<td>1.5-3.4 mg/dL</td>
<td>×10</td>
<td>15.34 mg/L</td>
</tr>
<tr>
<td><strong>THYROXINE, TOTAL, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-Term Infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 days</td>
<td>8.2-19.9 µg/dL</td>
<td>×12.9</td>
<td>106-256 nmol/L</td>
</tr>
<tr>
<td>1 wk</td>
<td>6.0-15.9 µg/dL</td>
<td>×12.9</td>
<td>77-205 nmol/L</td>
</tr>
<tr>
<td>1-12 mo</td>
<td>6.1-14.9 µg/dL</td>
<td>×12.9</td>
<td>79-192 nmol/L</td>
</tr>
<tr>
<td>Prepubertal Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 yr</td>
<td>6.8-13.5 µg/dL</td>
<td>×12.9</td>
<td>88-174 nmol/L</td>
</tr>
<tr>
<td>3-10 yr</td>
<td>5.5-12.8 µg/dL</td>
<td>×12.9</td>
<td>71-165 nmol/L</td>
</tr>
<tr>
<td>Pubertal Children and Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>4.2-13.0 µg/dL</td>
<td>×12.9</td>
<td>54-167 nmol/L</td>
</tr>
<tr>
<td><strong>THYROXINE, FREE, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-term (3 days)</td>
<td>2.0-4.9 ng/dL</td>
<td>×12.9</td>
<td>26-63.1 pmol/L</td>
</tr>
<tr>
<td>Infants</td>
<td>0.9-2.6 ng/dL</td>
<td>×12.9</td>
<td>12-33 pmol/L</td>
</tr>
<tr>
<td>Prepubertal children</td>
<td>0.8-2.2 ng/dL</td>
<td>×12.9</td>
<td>10-28 pmol/L</td>
</tr>
<tr>
<td>Pubertal children and adults</td>
<td>0.8-2.3 ng/dL</td>
<td>×12.9</td>
<td>10-30 pmol/L</td>
</tr>
<tr>
<td><strong>THYROXINE, TOTAL, WHOLE BLOOD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn screen (filter paper)</td>
<td>6.2-22.µg/dL</td>
<td>×12.9</td>
<td>80-283 nmol/L</td>
</tr>
<tr>
<td><strong>TRIODOOTHYRONINE, FREE, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>20-240 pg/dL</td>
<td>×0.01536</td>
<td>0.3-0.7 pmol/L</td>
</tr>
<tr>
<td>1-3 days</td>
<td>180-760 pg/dL</td>
<td>×0.01536</td>
<td>2.8-11.7 pmol/L</td>
</tr>
<tr>
<td>1-5 yr</td>
<td>185-770 pg/dL</td>
<td>×0.01536</td>
<td>2.8-11.8 pmol/L</td>
</tr>
<tr>
<td>5-10 yr</td>
<td>215-700 pg/dL</td>
<td>×0.01536</td>
<td>3.3-10.7 pmol/L</td>
</tr>
<tr>
<td>10-15 yr</td>
<td>230-650 pg/dL</td>
<td>×0.01536</td>
<td>3.5-10.0 pmol/L</td>
</tr>
<tr>
<td>&gt;15 yr</td>
<td>210-440 pg/dL</td>
<td>×0.01536</td>
<td>3.2-6.8 pmol/L</td>
</tr>
<tr>
<td><strong>TRIODOOTHYRONINE RESIN UPTAKE TEST (RTU), SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>26-36%</td>
<td>×0.01</td>
<td>0.26-0.36 fractional uptake</td>
</tr>
<tr>
<td>Thereafter</td>
<td>26-35%</td>
<td>×0.01</td>
<td>0.26-0.35 fractional uptake</td>
</tr>
<tr>
<td><strong>TRIODOOTHYRONINE, TOTAL, SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>30-70 ng/dL</td>
<td>×0.0154</td>
<td>0.46-1.08 nmol/L</td>
</tr>
<tr>
<td>1-3 days</td>
<td>75-260 ng/dL</td>
<td>×0.0154</td>
<td>1.16-4.00 nmol/L</td>
</tr>
<tr>
<td>1-5 yr</td>
<td>100-260 ng/dL</td>
<td>×0.0154</td>
<td>1.54-4.00 nmol/L</td>
</tr>
<tr>
<td>5-10 yr</td>
<td>90-240 ng/dL</td>
<td>×0.0154</td>
<td>1.39-3.70 nmol/L</td>
</tr>
<tr>
<td>10-15 yr</td>
<td>80-210 ng/dL</td>
<td>×0.0154</td>
<td>1.23-3.23 nmol/L</td>
</tr>
<tr>
<td>&gt;15 yr</td>
<td>115-190 ng/dL</td>
<td>×0.0154</td>
<td>1.77-2.93 nmol/L</td>
</tr>
</tbody>
</table>

Congenital hypothyroidism.

A, Absence of distal femoral epiphysis in a 3 mo old infant who was born at term. This is evidence for the onset of the hypothyroid state during fetal life. B, Epiphyseal dysgenesis in the head of the humerus in a 9 yr old girl who had been inadequately treated with thyroid hormone.

("beaking") of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X-rays of the skull show large fontanels and wide sutures; intersutural (wormian) bones are common. The sella turcica is often enlarged and round; in rare instances, there may be erosion and thinning. Formation and eruption of teeth can be delayed. Cardiac enlargement or pericardial effusion may be present.

Scintigraphy can help to pinpoint the underlying cause in infants with congenital hypothyroidism, but treatment should not be unduly delayed for this study. 123I-sodium iodide is superior to 99mTc-sodium pertechnetate for this purpose. Ultrasonographic examination of the thyroid is helpful, but studies show it can miss some ectopic glands shown by scintigraphy. Demonstration of ectopic thyroid tissue is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment with T4. Failure to demonstrate any thyroid tissue suggests thyroid aplasia, but this also occurs in neonates with hypothyroidism caused by maternal TRBAb and in infants with the iodide-trapping defect. A normally situated thyroid gland with a normal or avid uptake of radionuclide indicates a defect in thyroid hormone biosynthesis. In the past, patients with goitrous hypothyroidism have required extensive evaluation, including radiiodine studies, perchlorate discharge tests, kinetic studies, chromatography, and studies of thyroid tissue, to determine the biochemical nature of the defect. Most can be evaluated by genetic studies looking for a suspected mutation in the steps along the T4 biosynthetic pathway.

The electrocardiogram may show low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion. Echocardiography can confirm a pericardial effusion. The electroencephalogram often shows low voltage. In children older than 2 yr of age, the serum cholesterol level is usually elevated. Brain MRI before treatment is reportedly normal, although proton magnetic resonance spectroscopy shows high levels of choline-containing compounds, which can reflect blocks in myelin maturation.

**Treatment**

Levothyroxine (l-T4) given orally is the treatment of choice. Although T4 is the biologically active form of thyroid hormone, most of the T4 in the brain is formed from local deiodination of T3. Because 80% of circulating T4 is formed by monodeiodination of T3, serum levels of T4 and T3 return to normal with l-T4 treatment alone. The recommended initial starting dose is 10-15 µg/kg/day (totaling 37.5-50.0 µg/day for most term infants). The starting dose can be tailored to the severity of hypothyroidism. Rapid normalization of thyroid function has been demonstrated to be important in achieving optimal neurodevelopmental outcome. Newborns with more severe hypothyroidism, as judged by a serum T4 <5 µg/dL and/or imaging studies confirming aplasia, should be started at the higher end of the dosage range.

l-T4 is available only in tablet form in the United States; there is an approved liquid l-T4 preparation in Europe. The daily tablets should be crushed and mixed with a small volume of liquid. l-T4 tablets should not be mixed with soy protein formulas, concentrated iron, or calcium, because these can bind T4 and inhibit its absorption. Although it is recommended to administer l-T4 on an empty stomach and avoid food for 30-60 min, this is not practical in an infant. As long as the method of administration is consistent day to day, dosing can be adjusted based on serum thyroid test results to achieve the desired treatment goals.

Levels of serum T4 or free T4 and TSH should be monitored at recommended intervals (every 1-2 mo in the 1st 6 mo of life, and then every 2-4 mo between 6 mo and 3 yr of age). The goals of treatment are to maintain the serum free T4 or total T4 in the upper half of the reference range for age (see Table 565-2), with serum TSH in the reference range for age, optimally 0.5-2.0 mU/L. The dose of l-T4 on a weight basis gradually decreases with age.

Later, confirmation of the diagnosis may be necessary for some infants to rule out the possibility of transient hypothyroidism. This is unnecessary in infants with proven thyroid ectopia or in those who manifest elevated levels of TSH after 6-12 mo of therapy because of poor compliance or an inadequate dose of T4. Discontinuation of therapy at about 3 yr of age for 3-4 wk results in a marked increase in TSH levels in children with permanent hypothyroidism.

Care should be taken to avoid prolonged undertreatment or overtreatment. The only untoward effects of l-T4 are related to its dosage. Overtreatment can risk craniosynostosis and temperament problems.

**Prognosis**

Thyroid hormone is critical for normal cerebral development in the early postnatal months; biochemical diagnosis must be made soon after birth, and effective treatment must be initiated promptly to prevent irreversible brain damage. With the advent of neonatal screening programs for detection of congenital hypothyroidism, the prognosis for affected infants has improved dramatically. Early diagnosis and adequate treatment from the 1st weeks of life result in normal linear growth and development. Most studies report that psychometric testing in infants detected by newborn screening shows verbal, psychomotor, and global IQ scores similar to those of unaffected siblings or classmate controls. Some screening programs report that the most severely affected infants, as judged by the lowest T4 levels and retarded skeletal maturation, have reduced IQs (by 5-20 points) and other neuropsychologic sequelae, such as incoordination, hypotonia or hypertonia, short attention span, and speech problems, even with early diagnosis and treatment.
adequate treatment. Psychometric testing can show problems with vocabulary and reading comprehension, arithmetic, and memory. Approximately 20% of children have a neurosensory hearing deficit. Outcome studies in adults, detected and treated as neonates, reveal delayed social development, lower self-esteem, and a lower health-related quality of life. The latter appears to be related to those individuals with lower neurocognitive outcome and associated congenital malformations.

Delay in diagnosis, failure to correct initial hypothyroxinemia rapidly, inadequate treatment, and poor compliance in the 1st 2-3 yr of life result in variable degrees of brain damage. Without treatment, affected infants are profoundly intellectually challenged and growth retarded. When onset of hypothyroidism occurs after 2 yr of age, the outlook for normal development is much better even if diagnosis and treatment have been delayed, indicating how much more important thyroid hormone is to the rapidly growing brain of the infant.

**ACQUIRED HYPOTHYROIDISM**

**Epidemiology**

Studies of school-age children report that hypothyroidism occurs in approximately 0.3% (1 in 333). Subclinical hypothyroidism (TSH >4.5 mU/L, normal T₄ or free T₄) is more common, occurring in approximately 2% of adolescents. Acquired hypothyroidism is most commonly a result of chronic lymphocytic thyroiditis; 6% of children age 12-19 yr have evidence of autoimmune thyroid disease, which occurs with a 2:1 female: male preponderance.

**Etiology**

The most common cause of acquired hypothyroidism (Table 565-3) is chronic lymphocytic (Hashimoto) thyroiditis (see Chapter 566). Autoimmune thyroid disease may be part of polyglandular syndromes; children with Down and Turner syndrome, possibly Klinefelter syndrome, and celiac disease or diabetes are at higher risk for associated autoimmune thyroid disease (see Chapter 566) as are those with autoimmune polyglandular syndromes (APSs) (Tables 565-4 and 565-5). APS has 4 types, but APS-1 and APS-2 are the most common. APS-1 includes 2 components of the triad of hypoparathyroidism, Addison disease (adrenal insufficiency) and mucocutaneous candidiasis (“HAM” syndrome). Commonly referred to by the acronym APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia), it is autosomal recessive, caused by a mutation in the AIRE (autoimmune regulator) gene. Less-common features include thyroiditis (~10%), type 1 diabetes mellitus, primary hypogonadism, pernicious anemia, vitiligo, alopecia, chronic active hepatitis, and malabsorption syndrome. APS-2 (Schmidt syndrome) most commonly consists of autoimmune thyroiditis (~70%), Addison disease, and type 1 diabetes mellitus. Less-common features include primary hypogonadism, pernicious anemia, and vitiligo. APS-2 occurs more commonly than APS-1, generally presents in early adulthood, and has a female preponderance. The underlying immunologic defect remains to be determined.

---

**Table 565-3**  
Etiologic Classification of Acquired Hypothyroidism

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Hashimoto thyroiditis</th>
<th>Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced</td>
<td>Excess iodide: amiodarone, nutritional supplements, expectorants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants: phenytoin, phenobarbital, valproate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antithyroid drugs: methimazole, propylthiouracil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous: lithium, tyrosine kinase inhibitors, interferon alfa, stavudine, thalidomide, aminoglutethimide</td>
<td></td>
</tr>
<tr>
<td>Postablative</td>
<td>Irradiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radioiodine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thyroidectomy</td>
<td></td>
</tr>
<tr>
<td>Systemic infiltrative disease</td>
<td>Cystosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Langerhans cell histiocytosis</td>
<td></td>
</tr>
<tr>
<td>Hemangiomats (large) of the liver (type 3 iodothyronine deiodinase)</td>
<td>Hypothalamic-pituitary disease with multiple pituitary hormone deficiencies</td>
<td></td>
</tr>
<tr>
<td>Hypothalamic-pituitary tumors (e.g., craniopharyngioma)</td>
<td>Meningocerehalitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cranial radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Head trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Langerhans cell histiocytosis</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 565-4**  
Autoimmune Polyglandular Syndromes 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>APS-1</th>
<th>APS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>&lt;1 in 100,000 population/yr</td>
<td>1-2 in 10,000 population/yr</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Infancy/early childhood</td>
<td>Late childhood/adulthood</td>
</tr>
<tr>
<td><strong>Male : female ratio</strong></td>
<td>3:4</td>
<td>1:3</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Monogenic (AIRE gene)</td>
<td>Polygenic (HLA-associated)</td>
</tr>
<tr>
<td><strong>Mucocutaneous candidiasis</strong></td>
<td>73-100%</td>
<td>None</td>
</tr>
<tr>
<td><strong>Hyponadism</strong></td>
<td>Addiison disease</td>
<td>None</td>
</tr>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td>4-18%</td>
<td>41-52%</td>
</tr>
<tr>
<td><strong>Autoimmune thyroid disease</strong></td>
<td>8-40%</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Table 565-5**  
Organ-Specific Autoantigens in Autoimmune Polyglandular Syndromes

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>AUTOANTIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addision disease</td>
<td>P450c21, P450c17, P450c2c</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>Thyroid peroxidase, thyroglobulin</td>
</tr>
<tr>
<td>Graves disease</td>
<td>TSH receptor</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Calcium-sensing receptor, NALP 5 (NACHT leucine-rich-repeat protein 5)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Insulin, glutamic acid decarboxylase-65, IA-2A, ZnT8</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>P450c17, P450c2c</td>
</tr>
<tr>
<td>Immune gastritis</td>
<td>H+, K+-ATPase</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Intrinsic factor</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Transglutaminase, gliadin</td>
</tr>
<tr>
<td>Immune hepatitis</td>
<td>P450D6, P450D2c9, P4501A2</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>Tyrosine hydroxylase</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Tyrosinase</td>
</tr>
</tbody>
</table>

**Hypothesis**, thyrotropin; **TSH**, thyroid-stimulating hormone.

In children with Down syndrome, antithyroid antibodies develop in approximately 30%, and subclinical or overt hypothyroidism occurs in approximately 15-20%. In girls with Turner syndrome, antithyroid antibodies develop in approximately 40%, and subclinical or overt hypothyroidism occurs in approximately 15-30%, rising with increasing age. In children with type 1 diabetes mellitus, approximately 20% develop antithyroid antibodies and 5% become hypothyroid. Additional autoimmune diseases with an increased risk of hypothyroidism include immune dysregulation–polyendocrinopathy–enteropathy–X-linked syndrome (IPEX) and IPEX-like disorders, immunoglobulin G_{	ext{r}}-related diseases, Sjögren syndrome, multiple sclerosis, pernicious anemia, Addison disease, and ovarian failure. Although typically seen in adolescence, it occurs as early as in the 1st yr of life. Williams syndrome is associated with subclinical hypothyroidism; this does not appear to be autoimmune, as antithyroid antibodies are negative.

Protracted ingestion of medications containing iodides—for example, expectorants or nutritional supplements—can cause hypothyroidism, usually accompanied by goiter (see Chapter 567). Amiodarone, a drug used for cardiac arrhythmias and consisting of 37% iodine by weight, causes hypothyroidism in approximately 20% of treated children. It affects thyroid function directly by its high iodine content as well as by inhibition of 5’-deiodinase, which converts T4 to T3. Children treated with this drug should have serial measurements of T4, T3, and TSH.

Anticonvulsants, including phenytoin, phenobarbital, and valproate, may cause thyroid dysfunction, usually mild, subclinical hypothyroidism. Certain anticonvulsants stimulate hepatic P450 metabolism and excretion of T4. Children with Graves disease treated with antithyroid drugs (methimazole or propylthiouracil) can develop hypothyroidism. Additional drugs that can produce hypothyroidism include lithium, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, and aminoglutethimide.

Children who receive craniospinal irradiation, as with treatment of Hodgkin disease or other head and neck malignancies or that is administered before bone marrow transplantation, are at risk for thyroid damage. Approximately 30% of such children acquire elevated TSH levels within a year after therapy, and another 15-20% progress to hypothyroidism within 5-7 yr. Central (hypopituitary) hypothyroidism may develop in approximately 10% of children receiving craniospinal irradiation.

Radioactive iodine ablative treatment or thyroidectomy for Graves disease or cancer results in hypothyroidism, as can removal of ectopic thyroid tissue. Thyroid tissue in a thyroglossal duct cyst usually constitutes the only source of thyroid hormone, and excision results in hypothyroidism. Ultrasonographic examination or a radionuclide scan before surgery is indicated in these patients.

Children with nephroblastoma, a disorder characterized by intralysosomal storage of cystine in body tissues, acquire impaired thyroid function. Hypothyroidism may be overt, but subclinical forms are more common, and periodic assessment of TSH levels is indicated. By 13 yr of age, two thirds of these patients require T4 replacement.

Histiocytic infiltration of the thyroid in children with Langerhans cell histiocytosis (see Chapter 507) can result in hypothyroidism. Children with chronic hepatitis C infection are at risk for subclinical hypothyroidism; this does not appear to be autoimmune, because antithyroid antibodies are negative.

Hypothyroidism can occur in children with large hemangiomata of the liver, because of increased type 3 deiodinase activity, which catalyzes conversion of T4 to T3 and T3 to diiodothyronine. Thyroid secretion is increased, but it is not sufficient to compensate for the large increase in degradation of T4 to reverse T3.

Some patients with congenital thyroid dysgenesis and residual thyroid function or with incomplete genetic defects in thyroid hormone synthesis do not display clinical manifestations until childhood and appear to have acquired hypothyroidism. Although these conditions are usually now detected by newborn screening programs, very mild defects can escape detection.

Any hypothalamic or pituitary disease can cause acquired central hypothyroidism (see Chapter 557). TSH deficiency may be the result of a hypothalamic-pituitary tumor (craniopharyngioma is most common in children) or a result of treatment for the tumor. Other causes include cranial radiation, head trauma, or diseases infiltrating the pituitary gland, such as Langerhans cell histiocytosis.

Clinical Manifestations

Deceleration of growth is usually the first clinical manifestation, but this sign often goes unrecognized (Figs. 565-3 and 565-4). Goiter associated with Hashimoto thyroiditis, which may be a presenting feature, typically is nontender and firm, with a rubbery consistency and a pebbly surface. Weight gain is mostly fluid retention (myxedema), not true obesity. Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. Surprisingly, schoolwork and grades usually do not suffer, even in severely hypothyroid children. Additional features include bradycardia, muscle weakness or cramps, nerve entrapment, and ataxia. Osseous maturation is delayed, often strikingly, which is an indication of the duration of the hypothyroidism. Adolescents typically have delayed puberty; older adolescent girls manifest menometrorrhagia. Younger children might present with galactorrhea or pseudoprecocious puberty. Galactorrhea is a result of increased TRH stimulating prolactin secretion. The precocious puberty, characterized by breast development and vaginal bleeding in girls and macroorchidism in boys, is thought to be the result of abnormally high TSH concentrations binding to the follicle-stimulating hormone receptor with subsequent stimulation.

Some children have headaches and vision problems; they usually have enlargement of the pituitary gland, sometimes with suprasellar extension, after long-standing primary hypothyroidism. This condition, believed to be the result of thyrotroph hyperplasia, may be mistaken for a pituitary tumor (see Chapter 557). Abnormal laboratory studies include hypernatremia, macrocytic anemia, hypercholesterolemia, and elevated creatine phosphokinase. Table 565-6 lists the complications seen in severe hypothyroidism. All these changes return to normal with adequate replacement of T4.

Diagnostic Studies

Children with suspected hypothyroidism should undergo measurement of serum free T4 and TSH. Because the normal range for thyroid tests is slightly higher in children than adults, it is important to compare results to age-specific reference ranges. Measurement of anti-thyroglobulin and antiperoxidase antibodies can pinpoint autoimmune thyroiditis as the cause. In cases with a goiter resulting from autoimmune thyroid disease, an ultrasound examination typically shows diffuse enlargement with scattered hypechohogenicity. However, generally, sonography is not indicated unless there is a suspicion of a thyroid nodule on neck palpation. In such cases, ultrasound examination is the most accurate study to confirm the presence of a nodule and determine if other smaller nodules are present. In addition, an ultrasound examination can determine the nodule dimensions, texture (solid vs cystic nature), and presence or absence of other features that might influence a decision to undertake fine-needle aspiration, such as microcalcifications, blurred margins, “taller-than-wide” shape, intranodular vascular flow, and pathologic-appearing adjacent lymph nodes (see Chapter 569.1). In children with a nodule and suppressed TSH, a radioactive iodine uptake scan is indicated to determine if this is a “hot” or hyperfunctioning nodule. A bone age x-ray at diagnosis is useful, in that the degree of delay approximates duration and severity of hypothyroidism.

Treatment and Prognosis

L-T4 is the treatment of choice in children with hypothyroidism. The dose on a weight basis gradually decreases with age. For children age 1-3 yr, the average L-T4 dosage is 4-6 µg/kg/day; for age 3-10 yr, 3-5 µg/kg/day; and for age 10-16 yr, 2-4 µg/kg/day. Treatment should be monitored by measuring serum free T4 and TSH every 4-6 mo as well as 6 wk after any change in dosage. In children with central hypothyroidism, where TSH levels are not helpful in monitoring treatment, the goal should be to maintain serum free T4 in the upper half of the normal reference range for age.

During the 1st yr of treatment, deterioration of schoolwork, poor sleeping habits, restlessness, short attention span, and behavioral
Figure 565-3 A, Acquired hypothyroidism in a girl 6 yr of age. She was treated with a wide variety of hematinics for refractory anemia for 3 yr. She had almost complete cessation of growth, constipation, and sluggishness for 3 yr. The height age was 3 yr; the bone age was 4 yr. She had a sallow complexion and immature facies with a poorly developed nasal bridge. Serum cholesterol, 501 mg/dL; radioiodine uptake, 7% at 24 hr; protein-bound iodine (PBI), 2.8 mg/dL. B, After therapy for 18 mo, note the nasal development, increased luster and decreased pigmentation of hair, and maturation of the face. The height age was 5.5 yr; the bone age was 7 yr. There was a decided improvement in her general condition. Menarche occurred at 14 yr. The ultimate height was 155 cm (61 in). She graduated from high school. The disorder was well controlled with sodium-L-thyroxine daily.

Figure 565-4 A, Short stature (108 cm, <3rd percentile), generalized myxedema, sleepy expression, protuberant abdomen, and coarse hair are signs of hypothyroidism in this 12 yr old boy. Body proportions are immature for his age (1.25:1). B, Same boy 4 mo after treatment. His height increased by 4 cm; note the marked change in body habitus owing to loss of generalized myxedema, improved muscle tone, and bright facial expression. (From LaFranchi SH: Hypothyroidism, Pediatr Clin North Am 26:33-51, 1979.)

Table 565-6 Pathogenesis of General Complications in Management of Complicated Hypothyroidism

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Impaired ventricular systolic and diastolic functions and increased peripheral vascular resistance</td>
</tr>
<tr>
<td>Ventilatory failure</td>
<td>Blunted hypercapnic and hypoxic ventilatory drives</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Impaired renal free water excretion and syndrome of inappropriate antidiuretic hormone secretion</td>
</tr>
<tr>
<td>Ileus</td>
<td>Bowel hypomotility</td>
</tr>
<tr>
<td>Medication sensitivity</td>
<td>Reduced clearance rate and increased sensitivity to sedative, analgesic, and anesthetic agents</td>
</tr>
<tr>
<td>Hypothermia and lack of febrile response to sepsis</td>
<td>Decreased calorigenesis</td>
</tr>
<tr>
<td>Delirium, dementia, seizure, stupor, and coma</td>
<td>Decreased central nervous system thyroid hormone actions, and encephalopathy from hyponatremia and hypercapnia</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Associated intrinsic adrenal or pituitary disease, or reversible impairment of hypothalamic-pituitary-adrenal stress response</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Acquired von Willebrand syndrome (type 1) and decreased factors VIII, VII, V, IX, and X</td>
</tr>
</tbody>
</table>

problems might ensue, but these are transient; forewarning families about these manifestations enhances appropriate management. These may partially be ameliorated by starting at subreplacement T4 doses and advancing slowly. The development of persistent headaches or vision changes should prompt an evaluation for papilledema associated with pseudotumor cerebri, a rare complication following initiation of l-T4 treatment in older children (age 8-13 yr).

In older children, after catch-up growth is complete, the growth rate provides a good index of the adequacy of therapy. Periodic bone age x-rays are useful to monitor treatment and future growth potential. In children with long-standing hypothyroidism, catch-up growth may be incomplete (see Fig. 565-4). During the 1st 18 mo of treatment, skeletal maturation often exceeds expected linear growth, resulting in a loss of approximately 7 cm of predicted adult height.

Bibliography is available at Expert Consult.
CHRONIC LYMPHOCYTIC THYROIDITIS
(HASHIMOTO THYROIDITIS, AUTOIMMUNE THYROIDITIS)

Chronic lymphocytic thyroiditis is the most common cause of thyroid disease in children and adolescents and accounts for many of the enlarged thyroids formerly designated “adolescent” or “simple” goiter. It is also the most common cause of acquired hypothyroidism, with or without goiter.

One to 2% of younger school-age children and 6-8% of adolescents have positive antithyroid antibodies as evidence of autoimmune thyroid disease.

Etiology

This typical organ-specific autoimmune disease results from inheritance of susceptible genes involved in immunoregulation and environmental triggers, both as yet poorly characterized. Early in the course of the disease, there may be thyroid hyperplasia only; this is followed by infiltration of lymphocytes and plasma cells between the follicles and by atrophy of the follicles. Lymphoid follicle formation with germinal centers is almost always present; the degree of atrophy and fibrosis of the follicles varies from mild to moderate.

Intrathyroidal lymphocyte subsets differ from those in blood. Approximately 60% of infiltrating lymphoid cells are T cells, and approximately 30% express B-cell markers; the T-cell population is represented by helper (CD4+) and cytotoxic (CD8+) cells. The participation of cellular events in the pathogenesis is clear. Certain human leukocyte antigen (HLA) haplotypes (HLA-DR4, HLA-DR5) are associated with an increased risk of goiter and thyroiditis, and others (HLA-DR3) are associated with the atrophic variant of thyroiditis.

A variety of different thyroid antigen autoantibodies are also involved. Thyroid antiperoxidase antibodies (TPO-Abs) and antithyroglobulin antibodies (anti-Tg Abs) are demonstrable in the sera of 90% of children with chronic lymphocytic thyroiditis and in many patients with Graves disease. TPO-Abs are involved in activation of the complement cascade and in antibody-dependent, cell-mediated cytotoxicity. Anti-Tg Abs do not appear to play a role in the autoimmune destruction of the gland. Thyroid-stimulating hormone (TSH) receptor–blocking antibodies are related to the development of hypothyroidism and thyroid atrophy; they have been demonstrated in 18% of patients with severe hypothyroidism (TSH >20 mU/L) caused by autoimmune thyroiditis. Antibodies to pendrin, an apical protein on thyroid follicular cells, have been demonstrated in 80% of children with autoimmune thyroiditis. Antibodies also have been found against the sodium–iodide symporter, but their pathogenic role is unclear.

Clinical Manifestations

The disorder is 4-6 times more common in girls than in boys. It can occur during the 1st 3 yr of life, but becomes sharply more common after 6 yr of age and reaches a peak incidence during adolescence. The most common clinical manifestations are goiter and growth retardation. The goiter can appear insidiously and may be small or large. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In approximately 30% of patients, the gland is asymmetric and can seem to be nodular. Most of the affected children are clinically euthyroid and asymptomatic; some may have symptoms of pressure in the neck, including difficulty swallowing and shortness of breath. Some children have clinical signs of hypothyroidism, but others who appear clinically euthyroid have laboratory evidence of hypothyroidism. A few children have manifestations suggesting hyperthyroidism, such as nervousness, irritability, increased sweating, and hyperactivity, but results of laboratory studies are not necessarily those of hyperthyroidism. Occasionally, the disorder coexists with Graves disease (“Hashitoxicosis”). Ophthalmopathy can occur in autoimmune thyroiditis in the absence of Graves disease.

The clinical course is variable. The goiter might become smaller or might disappear spontaneously, or it might persist unchanged for years while the patient remains euthyroid. Most children who are euthyroid at presentation remain euthyroid, although a percentage of patients acquire hypothyroidism gradually within months or years. In children who initially have mild or subclinical hypothyroidism (elevated serum TSH, normal free thyroxine [T4] level), over several years approximately 40% revert to euthyroidism, 50% continue to have subclinical hypothyroidism, and approximately 10% develop overt hypothyroidism (elevated serum TSH, subnormal free T4 level). Chronic lymphocytic thyroiditis is the cause of most cases of nongoitrous (atrophic) hypothyroidism.

Familial clusters of chronic lymphocytic thyroiditis are common; the incidence in siblings or parents of affected children may be as high as 25%. TPO-Abs and anti-Tg Abs in these families appear to be inherited in an autosomal dominant fashion, with reduced penetrance in males. The concurrence within families of patients with chronic lymphocytic thyroiditis, hypothyroidism, and Graves disease provides cogent evidence for a basic relationship among these 3 conditions.

The disorder is associated with many other autoimmune disorders. Autoimmune thyroiditis occurs in 10% of patients with type I autoimmune polyglandular syndrome (APS-1), characterized by autoimmune polyclonar hypothyroidism, candidiasis, and ectodermal dysplasia (APECED). APS-1 consists of 2 of the triad of hypoparathyroidism, Addison disease, and mucocutaneous candidiasis (HAM syndrome). This relatively rare autosomal recessive disorder occurs in childhood and is caused by mutations in the autoimmune regulator (AIRE) gene on chromosome 21q22.3.

Autoimmune thyroid disease occurs in 70% of patients with APS-2. APS-2 consists of the association of autoimmune thyroiditis and Addison disease (Schmidt syndrome) or autoimmune thyroiditis with type 1 diabetes mellitus (Carpenter syndrome). It typically occurs in later childhood or early adulthood; the etiology is unknown. Autoimmune thyroiditis has been described in children with immunoneutralization polyendocrinopathy enteropathy X-linked (IPEX) syndrome, which includes early-onset diabetes and colitis. Autoimmune thyroid disease also tends to be associated with pernicious anemia, vitiligo, or alopecia. TPO-Abs are found in approximately 20% of white and 4% of black children with type 1 diabetes mellitus. Autoimmune thyroid disease has an increased incidence in children with congenital rubella.

Chronic lymphocytic thyroiditis also is associated with certain chromosomal disorders, particularly Turner syndrome and Down syndrome. In children with Down syndrome, one study reported that 28% had antithyroid antibodies (predominantly anti-TPOs), 7% had subclinical hypothyroidism, 7% had overt hypothyroidism, and 5% had
hyperthyroidism. In a study of girls with Turner syndrome, 41% had antithyroid antibodies (again, predominantly anti-TPOs), 18% had goiter, and 8% had subclinical or overt hyperthyroidism. Another study of 75 girls with Turner syndrome found that autoimmune thyroid disease increased from the 1st (15%) to the 3rd (30%) decade of life. Boys with Klinefelter syndrome appear to be at risk for autoimmune thyroid disease. Table 566-1 compares the characteristics of Hashimoto thyroiditis to other thyroiditis syndromes.

### Laboratory Findings
Thyroid function tests (free T₄ and TSH) are often normal, although the level of TSH may be slightly or even moderately elevated in some patients, which is termed subclinical hypothyroidism. That many children with chronic lymphocytic thyroiditis do not have elevated levels of TSH indicates that the goiter is caused by the lymphocytic infiltration or by thyroid growth-stimulating immunoglobulins. Young children with chronic lymphocytic thyroiditis have serum TPO-Abs, but the anti-Tg Abs are positive in <50%. TPO-Abs and anti-Tg Abs are found equally in adolescents with chronic lymphocytic thyroiditis. When both tests are used, approximately 95% of patients with thyroid autoimmunity are detected. Levels in children and adolescents are lower than those in adults with Hashimoto thyroiditis, and repeated measurements are indicated in questionable instances because titers might increase later in the course of the disease. In adolescent females with overt hypothyroidism, measurement of TSH receptor–blocking antibodies may identify patients at future risk of having babies with transient congenital hypothyroidism.

Thyroid scans and ultrasonography usually are not needed. If they are done, thyroid scans reveal irregular and patchy distribution of the radioisotope, and in approximately 60% or more, the administration of perchlorate results in a >10% discharge of iodide from the thyroid gland. Thyroid ultrasonography shows heterogeneous echogenicity in most patients, along with an increased number of benign-appearing hyperplastic lymph nodes in the neck. The definitive diagnosis can be established by biopsy of the thyroid; this procedure is rarely clinically indicated.

Antithyroid antibodies also may be found in almost 50% of the siblings of affected patients and in a significant percentage of the mothers of children with Down syndrome or Turner syndrome without demonstrable thyroid disease.

### Treatment
If there is evidence of overt hypothyroidism (elevated TSH, low T₄, or free T₄), replacement treatment with levothyroxine (at doses specific for size and age) is indicated. The goiter usually shows some decrease in size but can persist for years. In a euthyroid patient, treatment with suppressive doses of levothyroxine is unlikely to lead to a significant decrease in size of the goiter. Antibody levels fluctuate in both treated and untreated patients and persist for years. Because the disease is self-limited in some instances, the need for continued therapy requires periodic reevaluation. Untreated patients should also be checked periodically. Although there is some controversy about treating patients with subclinical hypothyroidism (elevated TSH, normal T₄, or free T₄), many clinicians prefer to treat such children until growth and puberty are complete, and then reevaluate their thyroid function.

Prominent nodules (i.e., >1 cm) that persist despite suppressive therapy should be examined histologically using fine-needle aspiration, because thyroid carcinoma or lymphoma has occurred in patients with Hashimoto thyroiditis.

### Other Causes of Thyroiditis
Subacute granulomatous thyroiditis (de Quervain disease) is rare in children. It is thought to have a viral cause and remits spontaneously. The disorder becomes manifested by an upper respiratory infection with vague tenderness over the thyroid and low-grade fever, followed by severe pain in the region of the thyroid gland. Inflammation results in leakage of preformed thyroid hormone from the gland into the circulation. Serum levels of T₄ and triiodothyronine are elevated while TSH is suppressed, and mild symptoms of hyperthyroidism may be present, but radioiodine uptake is depressed. The erythrocyte sedimentation rate is increased. The course is variable but usually characterized by 4 phases: hyperthyroidism, usually followed by a euthyroid phase and then a hypothyroid phase, and remission usually occurring in several months, with recovery to euthyroidism.

Acute suppurative thyroiditis is uncommon in children; it is usually preceded by a respiratory infection with pharyngitis. The left lower lobe is affected predominantly. Abscess formation can occur; anaerobic organisms, with or without aerobes, are the typical infectious agents. The most common organism is α-hemolytic streptococci (viridans) followed by *Staphylococcus aureus* and pneumococci. Recurrent episodes or detection of a mixed bacterial flora suggests that the infection arises from a *piriform sinus fistula* or, less commonly, from a thyroglossal duct remnant. Exquisite tenderness of the gland, swelling, erythema, dysphagia, and limitation of head motion are characteristic findings. Fever, chills, and sore throat are not uncommon, and leukocytosis is present. Scintigrams of the thyroid often reveal decreased uptake in the affected areas, and ultrasonography might show a complex echogenic mass. Thyroid function is usually normal, but hyperthyroidism caused by escape of thyroid hormone has been encountered in a child with suppurative thyroiditis resulting from *Aspergillus*. When abscesses form, incision and drainage and administration of parenteral antibiotics are indicated. After the infection

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**Table 566-1** Characteristics of Thyroiditis Syndromes

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>HASHIMOTO THYROIDITIS</th>
<th>PAINLESS POSTPARTUM THYROIDITIS</th>
<th>PAINLESS SPORADIC THYROIDITIS</th>
<th>PAINFUL SUBACUTE THYROIDITIS</th>
<th>ACUTE SUPPURATIVE THYROIDITIS</th>
<th>RIEDEL THYROIDITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (F:M)</td>
<td>4:6:1</td>
<td>—</td>
<td>2:1</td>
<td>5:1</td>
<td>1:1</td>
<td>3:4:1</td>
</tr>
<tr>
<td>Cause</td>
<td>Autoimmune</td>
<td>Autoimmune</td>
<td>Autoimmune</td>
<td>Unknown (probably viral)</td>
<td>Infectious (bacterial)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pathologic findings</td>
<td>Lymphocytic infiltration, germinal centers, fibrosis</td>
<td>Lymphocytic infiltration</td>
<td>Lymphocytic infiltration</td>
<td>Giant cells, granulomas</td>
<td>Abscess formation</td>
<td>Dense fibrosis</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>Usually euthyroidism; some hypothyroidism</td>
<td>Hyperthyroidism, hypothyroidism, or both</td>
<td>Hyperthyroidism, hypothyroidism, or both</td>
<td>Hyperthyroidism, hypothyroidism, or both</td>
<td>Usually euthyroidism</td>
<td>Usually euthyroidism</td>
</tr>
<tr>
<td>TPO antibodies</td>
<td>High titer, persistent</td>
<td>High titer, persistent</td>
<td>High titer, persistent</td>
<td>Low titer, or absent, or transient</td>
<td>Absent</td>
<td>Usually present</td>
</tr>
<tr>
<td>ESR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>24 hr ¹²³I uptake</td>
<td>Variable</td>
<td>Normal</td>
<td>Normal</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>Normal</td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; ¹²³I, iodine 123; TPO, thyroid peroxidase.

subsides, a barium esophagram or CT scan with contrast is indicated
to search for a fistulous tract; if one is found, surgical excision is
indicated.

Specific conditions such as tuberculosis, sarcoidosis, mumps, and
cat-scratch disease are rare causes of thyroiditis in children. Other
forms of thyroiditis seen in adults, such as painless sporadic thyroid-
itis and Riedel thyroiditis, are rare in children (see Table 566-1).

Bibliography is available at Expert Consult.
Bibliography
Goiter

Stephen A. Huang and Stephen H. LaFranchi

A goiter, or thyromegaly, is an enlargement of the thyroid gland. Persons with enlarged thyroids can have normal function of the gland (euthyroidism), thyroid deficiency (hypothyroidism), or overproduction of the hormones (hyperthyroidism). Goiter may be congenital or acquired, endemic or sporadic. Detection of a goiter should prompt an investigation of its cause and the assessment of thyroid function.

Goiter most often results from the increased pituitary secretion of thyroid-stimulating hormone (TSH) in response to decreased circulating levels of thyroid hormones. Activation of the TSH receptor from thyrotropin receptor-stimulating antibodies (in Graves disease), gain-of-function TSH receptor mutations, or inappropriate TSH secretion (from dominant negative thyroid hormone receptor mutations or TSH-secreting adenomas) can also cause thyromegaly. Thyroid enlargement can also result from infiltrative processes that may be inflammatory or neoplastic.

567.1 Congenital Goiter

Stephen A. Huang and Stephen H. LaFranchi

Congenital goiter is usually sporadic and can result from a fetal thyroxine (T4) synthetic defect or from administration of antithyroid drugs or iodides during pregnancy for the treatment of maternal thyrotoxicosis. Goitrogenic drugs that cross the placenta at high doses can interfere with synthesis of thyroid hormone, resulting in goiter and hypothyroidism in the fetus. These effects are most severe when pharmacologic overtreatment with antithyroid drugs causes concomitant hypothyroidism in the mother and reduces the supply of maternal thyroid hormone available to the fetus. In women with Graves disease receiving antithyroid drugs, fetal effects can occur when the mother takes propylthiouracil at only 100-200 mg/24 hr; consequently, all infants born to women treated with antithyroid drugs in the 3rd trimester should undergo thyroid studies at birth. Even when the infant is clinically euthyroid, there may be retardation of osseous maturation, low levels of T4, and elevated levels of TSH. Administration of thyroid hormone to affected infants may be indicated to treat clinical hypothyroidism, to hasten the disappearance of the goiter, and to prevent brain damage. Because the condition is rarely permanent, thyroid hormone may be safely discontinued after the antithyroid drug has been excreted by the neonate, usually after 1-2 wk. In addition to antithyroid medications, iodides are included in many proprietary cough preparations used to treat asthma; these preparations should be avoided during pregnancy because they have often been reported to cause congenital goiter. Amiodarone, an antiarrhythmic drug with 37% iodine content, has also caused congenital goiter with hypothyroidism.

Enlargement of the thyroid at birth may occasionally be sufficient to cause respiratory distress that interferes with nursing and can even cause death. The head may be maintained in extreme hyperextension. In pregnant women who are overtreated with antithyroid drugs, the prenatal diagnosis of even massive fetal goiter can often be corrected by withdrawal of the maternal medication, with or without intranasal thyroid hormone injection. When postnatal respiratory obstruction is severe, partial thyroidectomy rather than tracheostomy is indicated (Fig. 567-1).

Goiter is almost always present in the infant with neonatal Graves hyperthyroidism. Thyroid enlargement results from transplacental passage of maternal thyroid-stimulating immunoglobulin (see Chapter 568.2). These goiters usually are not large; the infant manifests clinical symptoms of hyperthyroidism. The mother often has a history of Graves disease, or the diagnosis of maternal Graves may be revealed through the evaluation of neonatal hyperthyroidism. TSH receptor-activating mutations are also a recognized cause of congenital goiter and hyperthyroidism.

When no causative factor is identifiable from the maternal or medication history, a defect in synthesis of thyroid hormone should be suspected. Neonatal screening programs find congenital hypothyroidism caused by such a defect in 1 in 30,000-50,000 live births. It is advisable to treat immediately with thyroid hormone and to postpone more-detailed studies for later in life. If a specific defect is suspected,
genetic tests to identify a mutation may be undertaken (see Chapter 565). Because these defects are often caused by recessive mutations, a precise diagnosis is helpful for genetic counseling. Monitoring subsequent pregnancies with ultrasonography can be useful in detecting fetal goiters (see Chapter 96).

**Pendred syndrome**, characterized by familial goiter and neurosensory deafness, is caused by a mutation in the SLC26A4 gene, which encodes the pendrin chloride–iodide transport protein expressed in the thyroid gland and cochlea. This defect results in abnormal iodide organification in the thyroid and can cause a goiter at birth. The more common presentation is a euthyroid goiter and sensorineural hearing loss later in life.

**Iodine deficiency** as a cause of congenital goiter is rare in developed countries but persists in isolated endemic areas (see Chapter 567.3). More important is the recognition that severe iodine deficiency early in pregnancy can cause neurologic damage during fetal development, even in the absence of goiter. The iodine deficiency can result in combined maternal and fetal hypothyroidism, reducing the protective transfer of maternal thyroid hormones.

When the “goiter” is lobulated, asymmetric, firm, or large to an unusual degree, a teratoma within or in the vicinity of the thyroid must be considered in the differential diagnosis (see Chapter 569).

**Bibliography is available at Expert Consult.**

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**567.2 Intratracheal Goiter**  
*Stephen A. Huang and Stephen H. LaFranchi*

One of the many ectopic locations of thyroid tissue is within the trachea. The intraluminal thyroid lies beneath the tracheal mucosa and is often continuous with the normally situated extratracheal thyroid gland. The thyroid is susceptible to goitrous enlargement, which involves both the eutopic and ectopic thyroid tissue. When there is obstruction of the airway associated with a goiter, it must be ascertained whether the obstruction is extratracheal or endotracheal. If obstructive manifestations are mild, administration of sodium L-thyroxine (levothyroxine) usually causes the goiter to decrease in size. When symptoms are severe, surgical removal of the endotracheal goiter is indicated.

**567.3 Endemic Goiter and Cretinism**  
*Stephen A. Huang and Stephen H. LaFranchi*

**ETIOLOGY**

The association between dietary deficiency of iodine and the prevalence of goiter or cretinism is well established. A moderate deficiency of iodine can be overcome by increased efficiency in the synthesis of thyroid hormone. Iodine liberated in the tissues is returned rapidly to the thyroid. Demand for the hormone is satisfied by compensatory hypertrophy and hyperplasia (goiter), which satisfy the demands of the tissues for thyroid hormone. In geographic areas where deficiency of iodine is severe, decompensation and hypothyroidism can result. Recent estimates from the World Health Organization indicate that nearly 2 billion individuals currently have insufficient iodine intake, including one third of the world’s school-age children. Thus, despite great progress in the global effort to reduce iodine deficiency, it remains the leading cause of preventable intellectual disability worldwide.

Seawater is rich in iodine; the iodine content of fish and shellfish is also high. As a result, endemic goiter is rare in populations living along the coast. Iodine is deficient in the water and native foods in the Pacific West and the Great Lakes areas of the United States. Deficiency of dietary iodine is even greater in certain Alpine valleys, the Himalayas, the Andes, the Congo, and the highlands of Papua New Guinea. In areas such as the United States, where iodine is provided in foods from other areas and in iodized salt, endemic goiter has disappeared. Iodized salt in the United States contains potassium iodide (100 µg/g), which provides excellent prophylaxis. Further iodine intake in the United States is contributed by iodates used in baking, iodine-containing coloring agents, and iodine-containing disinfectants used in the dairy industry. The recommended daily allowance of iodine is as follows:

- Children younger than 2 yr: ≥100 µg/day
- School-age children: 100–299 µg/day
- Pregnant women: ≥150 µg/day
- Lactating women: ≥100 µg/day

While the overall dietary iodine intake in the United States is considered adequate, the most recent NHANES (National Health and Nutrition Examination Survey) from 2007-2010 reports that the median urinary iodine concentration among pregnant U.S. women has dropped to <150 µg/L. This indicates mild iodine deficiency and highlights the risk of iodine deficiency reemergence in industrialized countries as salt intake decreases. These risks can be mitigated by the continued monitoring of iodine status, the adjustment of salt iodization levels, and the targeted supplementation of vulnerable subpopulations (promotion of iodine-containing prenatal vitamins).

**CLINICAL MANIFESTATIONS**

If the deficiency of iodine is mild, thyroid enlargement does not become noticeable except when there is increased demand for the hormone during periods of rapid growth, as in adolescence and during pregnancy. In regions of moderate iodine deficiency, goiter observed in school children can disappear with maturity and reappear during pregnancy or lactation. Iodine-deficient goiters are more common in girls than in boys. In areas where iodine deficiency is severe, as in the hyperendemic highlands of Papua New Guinea, nearly half the population has large goiters, and endemic cretinism is common (Fig. 567-2).

![Figure 567-2 A 14 yr old boy with a large nodular goiter was seen in 2004, in an area of severe iodine-deficiency disorders in northern Morocco. He had tracheal and esophageal compression and hoarseness, probably as a result of damage to the recurrent laryngeal nerves. (From Zimmermann MB, Jooste PL, Pandav CS: Iodine-deficiency disorders, Lancet 372:1251–1262, 2008, Fig 2.)](image-url)
Bibliography

Serum T₄ levels are often low in persons with endemic goiter, although clinical hypothyroidism is rare. This is true in New Guinea, the Congo, the Himalayas, and South America. Despite low serum T₄ levels, serum TSH concentrations are often normal or only moderately increased. In such patients, circulating levels of T₃ are elevated. Moreover, T₄ levels are also elevated in patients with normal T₃ levels, indicating a preferential secretion of T₃ by the thyroid in this disease and an adaptive increase in peripheral T₃ to T₄ conversion.

Endemic cretinism is the most serious consequence of iodine deficiency; it occurs only in geographic association with endemic goiter. The term endemic cretinism includes 2 different but overlapping syndromes: a neurologic type and a myxedematous type. The incidence of the 2 types varies among different populations. In Papua New Guinea, the neurologic type occurs almost exclusively, whereas in the Congo, the myxedematous type predominates. Both types are found in all endemic areas, and some persons have intermediate or mixed features.

The neurologic syndrome is characterized by intellectual disability, deaf-mutism, disturbances in standing and gait, and pyramidal signs such as clonus of the foot, the Babinski sign, and patellar hyperreflexia. Affected persons are goitrous but euthyroid, have normal pubertal development and adult stature, and have little or no impaired thyroid function. Persons with the myxedematous syndrome also are intellectually challenged and deaf and have neurologic symptoms, but in contrast to the neurologic type, they have delayed growth and sexual development, myxedema, and absence of goiter. Serum T₄ levels are low and TSH levels are markedly elevated. Delayed skeletal maturation may extend into the 3rd decade or later. Ultrasonographic examination shows thyroid atrophy.

**PATHOGENESIS**

The pathogenesis of the neurologic syndrome is attributed to iodine deficiency and hypothyroxinemia during pregnancy, leading to fetal and postnatal hypothyroidism. Although some investigators have attributed brain damage to a direct effect of elemental iodine deficiency in the fetus, most believe the neurologic symptoms are caused by combined fetal and maternal hypothyroxinemia. There is evidence for the presence of thyroid hormone receptors in the fetal brain as early as 7 wk of gestation. Although the normal fetal thyroid gland does not begin to produce significant amounts of thyroid hormone until midgestation, there is measurable T₄ in the coelomic fluid as early as 6 wk, almost certainly of maternal origin. These lines of evidence support a role for maternal thyroid hormone in fetal brain development in the 1st trimester. In addition, there is evidence of transplacental passage of maternal thyroid hormone into the fetus, which normally might ameliorate the effects of fetal hypothyroidism on the developing nervous system in the second half of pregnancy. Thus, iodine deficiency in the mother affects fetal brain development both in the 1st trimester and throughout pregnancy. Intake of iodine after birth is often sufficient for normal or only minimally impaired thyroid function.

The pathogenesis of the myxedematous syndrome leading to thyroid atrophy is more bewildering. Searches for additional environmental factors that might provoke continuing postnatal hypothyroidism have led to incrimination of selenium deficiency, goitrogenic foods, thiocyanates, and *Yersinia* (Table 567-1). Studies from western China suggest that thyroid autoimmunity might play a role. Children with myxedematous cretinism with thyroid atrophy, but not children with euthyroid cretinism, were found to have thyroid growth-blocking immunoglobulins of the kind found in infants with sporadic congenital hypothyroidism. Others are skeptical about any role of thyroid growth-blocking immunoglobulins to explain these findings.

**TREATMENT**

In many developing countries, administration of a single intramuscular injection of iodinated poppy seed oil to women prevents iodine deficiency during future pregnancies for approximately 5 yr. This form of therapy given to children younger than 4 yr of age with myxedematous cretinism results in a euthyroid state in 5 mo. Older children respond poorly and adults not at all to iodized oil injections, indicating an inability of the thyroid gland to synthesize hormone; these patients require treatment with T₄. Through the efforts of the World Health Organization and its program of universal salt iodization, the number of households worldwide with access to adequately iodized salt has increased from <10% in 1990 to 70% in 2012. In the Xinjiang province of China, where the usual methods of iodine supplementation had failed, iodination of irrigation water has increased iodine levels in soil, animals, and human beings. In other countries, iodinated salt in school meal programs gives children the dietary iodine they need. Still, political, economic, and practical obstacles have limited penetration of iodized food into regular diets around the world.

**Bibliography is available at Expert Consult.**

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**Table 567-1**

<table>
<thead>
<tr>
<th>GOITROGEN MECHANISM</th>
<th>GOITROGENS and Their Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOODS</strong></td>
<td>Cassava, lima beans, linseed, sorghum, sweet potato</td>
</tr>
<tr>
<td></td>
<td><strong>Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid</strong></td>
</tr>
<tr>
<td>Cruciferous vegetables such as cabbage, kale, cauliflower, broccoli, turnips, rapeseed</td>
<td><strong>Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid</strong></td>
</tr>
<tr>
<td>Soy, millet</td>
<td><strong>Flavonoids impair thyroid peroxidase activity</strong></td>
</tr>
<tr>
<td><strong>INDUSTRIAL POLLUTANTS</strong></td>
<td>Perchlorate</td>
</tr>
<tr>
<td></td>
<td><strong>Competitive inhibitor of the sodium-iodine symporter, decreasing iodine transport into the thyroid</strong></td>
</tr>
<tr>
<td>Others (e.g., disulfides from coal processes)</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td><strong>An important goitrogen; smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast</strong></td>
</tr>
</tbody>
</table>

**NUTRIENTS**

| Selenium deficiency | Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation |
| Iron deficiency | Reduces heme-dependent thyroperoxidase activity in the thyroid and might blunt the efficacy of iodine prophylaxis |
| Vitamin A deficiency | Increases TSH stimulation and goiter through decreased vitamin A-mediated suppression of the pituitary TSH-β gene |

TSH, thyroid-stimulating hormone.


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567.4 Acquired Goiter

Stephen A. Huang and Stephen H. LaFranchi

Most acquired goiters are sporadic and develop from a variety of causes; patients are usually euthyroid but may be hypothyroid or hyperthyroid. The most common cause of acquired goiter is...
Bibliography
lymphocytic thyroiditis (see Chapter 566). Rarer causes in children include painless sporadic thyroiditis and substernal painful thyroiditis (de Quervain disease; see Chapter 566). Other causes include excess iodide ingestion and certain drugs, including amiodarone and lithium. Intrinsic biochemical defects in the synthesis of thyroid hormone are almost always associated with goiter; thymemalgia from milder defects occurs later in childhood. The occurrence of the disorder in siblings, onset in early life, and possible association with hypothyroidism (goitrous hypothyroidism) are important clues to the diagnosis.

**IODIDE GOITER**

A small percentage of patients treated with iodide preparations for prolonged periods acquire goiters. Iodides are commonly included for their expectorant effect in cough medicines and in proprietary mixtures for asthma. Goiters resulting from iodide administration are firm and diffusely enlarged, and in some instances hypothyroidism develops. In normal persons, acute administration of large doses of iodide inhibits the organification of iodine and the synthesis of thyroid hormone (Wolff-Chaikoff effect). This effect is short-lived and does not lead to permanent hypothyroidism. When iodide administration continues, an autoregulatory mechanism in normal persons limits iodide trapping and permits the level of iodide in the thyroid to decrease and organification to proceed normally. In patients with iodide-induced goiter, this escape does not occur, because of an underlying abnormality of biosynthesis of thyroid hormone. The persons most susceptible to the development of iodide goiter are those with lymphocytic thyroiditis or with a subclinical inborn error in thyroid hormone synthesis and those who have had a partial thyroidectomy.

**Lithium carbonate**, which is used to treat bipolar disorder, also causes goiters and mild hypothyroidism. Lithium decreases $T_4$ and $T_3$ synthesis and release; the mechanism producing the goiter or hypothyroidism is similar to that described for iodide goiter. Lithium and iodide also act synergistically to produce goiter; their combined use should be avoided.

**Amiodarone**, a drug used to treat cardiac arrhythmias, can cause thyroid dysfunction with goiter because it is rich in iodine. It is also a potent inhibitor of 5'-deiodinase, preventing conversion of $T_4$ to $T_3$. It can cause hypothyroidism, particularly in patients with underlying autoimmune disease. In other patients, it can cause thyrotoxicosis through either transient thyroiditis or the Jod-Basedow effect.

**SIMPLE GOITER (COLLOID GOITER)**

A few children with euthyroid goiters have simple goiters, a condition of unknown cause not associated with hypothyroidism or hyperthyroidism and not caused by inflammation or neoplasia. The condition predominates in girls and has a peak incidence before and during the pubertal years. Histologic examination of the thyroid either is normal or reveals variable follicular size, dense colloid, and flattened epithelium. The goiter may be small or large. It is firm in half the patients and occasionally is asymmetric or nodular. Levels of TSH are normal or low, scintiscans are normal, and thyroid antibodies are absent. Differentiation from lymphocytic thyroiditis might not be possible without a biopsy, but biopsy is usually not indicated. Therapy with thyroid hormone can help prevent progression to a large multinodular goiter, although it is difficult to separate any treatment effects from the natural history, which is for the goiter to decrease in size. Patients should be reevaluated periodically, because some have antibody-negative lymphocytic thyroiditis and therefore are at risk for changes in thyroid function (see Chapter 566).

**MULTINODULAR GOITER**

Rarely, a firm goiter with a lobulated surface and single or multiple palpable nodules is encountered. Areas of cystic change, hemorrhage, and fibrosis may be present. The incidence of this condition has decreased markedly with the use of iodine-enriched salt. A mild goitrogenic stimulus, acting over a long time, is thought to be the cause. Ultrasonographic examination can reveal multiple nodules that are nonfunctioning on scintiscans. Thyroid studies are usually normal. Some children with chronic lymphocytic thyroiditis develop multinodular goiter; TSH may be elevated, and thyroid antibodies may be present.

Children can develop toxic multinodular goiter, characterized by a suppressed TSH and hyperthyroidism. The condition occurs in children with McCune-Albright syndrome (usually resulting in hyperthyroidism), with TSH receptor–activating mutations, and it has been described in 3 children (including 2 siblings) with digital anomalies and cystic kidney disease. If hypofunctioning nodules within a multinodular goiter grow to significant size ($\geq 1$ cm), fine-needle aspiration should be considered to rule out malignancy (see Chapter 569).

**TOXIC GOITER (HYPERTHYROIDISM)**

See Chapter 568.

*Bibliography is available at Expert Consult.*
Bibliography


Hyperthyroidism results from excessive secretion of thyroid hormone; during childhood, with few exceptions, it is caused by Graves disease (Table 568-1). Graves disease is an autoimmune disorder; production of thyroid-stimulating immunoglobulin that binds to and activates the G-protein–coupled thyroid-stimulating hormone (TSH) receptor results in diffuse toxic goiter. Other causes of hyperthyroidism include gain-of-function germline mutations in the TSH receptor, which are found in both familial (autosomal dominant) and sporadic cases of non–autoimmune hyperthyroidism. These patients, whose disease can appear in the neonatal period or in later childhood, have thyroid hyperplasia with goiter and suppressed levels of TSH. Different activating mutations have been identified in some cases of thyroid adenomas. Hyperthyroidism occurs in some patients with McCune-Albright syndrome as a result of an activating mutation of the α subunit of the G-protein; these patients tend to have a multinodular goiter. Other rare causes of thyrotoxicosis that have been observed in children include painless sporadic thyroiditis, subacute painful thyroiditis, acute suppurative thyroiditis, thyrotoxicosis factitia, TSH-secreting adenomas, and hyperfunctioning thyroid carcinoma.

Suppression of plasma TSH indicates that the hyperthyroidism is not pituitary in origin. Hyperthyroidism caused by inappropriate thyrotropin secretion is rare and, in most cases, is caused by dominant negative thyroid hormone receptor mutations and pituitary resistance to thyroid hormone. TSH-secreting pituitary tumors are extremely rare in the pediatric population. In infants born to mothers with Graves disease, hyperthyroidism is almost always a transitory phenomenon; classic Graves disease during the neonatal period is rare. Choriocarcinoma, hydatidiform mole, and struma ovarii have caused hyperthyroidism in adults but have not been recognized as causes in children.

Studies have examined the health and quality of life of individuals with subclinical hyperthyroidism (i.e., with TSH <0.1 mU/L, but normal serum thyroxine [T4] and triiodothyronine [T3] concentrations) or who are euthyroid on antithyroid medication. These studies indicate that subclinical hyperthyroidism carries a risk of late-life atrial fibrillation, but no similar risks have been identified in the general pediatric population. There appears to be no difference in long-term quality of life among hyperthyroid patients treated with antithyroid medication, radioiodine ablation, or surgery. Quality of life was diminished relative to control persons in all 3 cases (see Chapter 568.1).
Graves Disease

**EPIDEMIOLOGY**
Graves disease occurs in approximately 0.02% of children (1:5,000). It has a peak incidence in the 11-15 yr old age group; there is a 5:1 female : male ratio. Most children with Graves disease have a positive family history of some form of autoimmune thyroid disease. In Japan, familial Graves disease, defined as Graves disease in a 1st-degree relative, occurs in 2-3% of cases.

**ETIOLOGY**
Enlargement of the thymus, splenomegaly, lymphadenopathy, infiltration of the thyroid gland and retroorbital tissue with lymphocytes and plasma cells, and peripheral lymphocytosis are well-established findings in Graves disease. In the thyroid gland, T-helper cells (CD4+), predominate in dense lymphoid aggregates; in areas of lower cell density, cytotoxic T cells (CD8+) predominate. The percentage of activated B lymphocytes infiltrating the thyroid is higher than in peripheral blood. A postulated failure of T-suppressor cells allows expression of T-helper cells, sensitized to the TSH antigen, which interact with B cells. These cells differentiate into plasma cells, which produce thyrotropin receptor–stimulating antibody (TRSAb). TRSAb binds to the receptor for TSH and stimulates cyclic adenosine monophosphate, resulting in thyroid hyperplasia and unregulated overproduction of thyroid hormone. In addition to TRSAb, thyrotropin receptor–blocking antibody (TRBAb), which binds but does not activate the TSH receptor, may also be produced, and the clinical course of the disease usually correlates with the ratio between the 2 antibodies.

The ophthalmopathy occurring in Graves disease appears to be caused by antibodies against antigens shared by the thyroid and eye muscle. TSH receptors have been identified in retroorbital adipocytes and might represent a target for antibodies. The antibodies that bind to the extracellular muscles and orbital fibroblasts stimulate the synthesis of glycosaminoglycans by orbital fibroblasts and produce cytotoxic effects on muscle cells.

In whites, Graves disease is associated with human leukocyte antigen (HLA)-B8 and HLA-DR3; the latter carries a 7-fold relative risk for Graves disease. Graves disease is also associated with other HLA-D3-related disorders, such as Addison disease, type 1 diabetes mellitus, myasthenia gravis, and celiac disease. Systemic lupus erythematosus, rheumatoid arthritis, vitiligo, idiopathic thrombocytopenic purpura, and pernicious anemia have been described in children with Graves disease. In family clusters, the conditions associated most commonly with Graves disease are autoimmune lymphocytic thyroiditis and hypothyroidism. In Japanese children, Graves disease is associated with different HLA haplotypes: HLA-DRB1*0405 and HLA-DQB1*0401. In the Chinese population, the RNASET2-FGFR1OP-CCR6 region at 6q27 and an intergenic region at 4p14 are important susceptibility loci.

**CLINICAL MANIFESTATIONS**
Approximately 5% of all patients with hyperthyroidism are younger than 15 yr of age; the peak incidence in these children occurs during adolescence. Although rare, Graves disease has begun between 6 wk and 2 yr of age in children born to mothers without a history of hyperthyroidism. The incidence is approximately 5 times higher in girls than in boys.

The clinical course in children is highly variable but usually is not so fulminant as in many adults (Table 568-2). Symptoms develop gradually; the usual interval between onset and diagnosis is 6-12 mo and may be longer in prepubescent children compared with adolescents. The earliest signs in children may be emotional disturbances accompanied by motor hyperactivity. The children become irritable and excitable, and they cry easily because of emotional lability. They are restless sleepers and tend to kick their covers off. Their schoolwork suffers as a result of a short attention span and poor sleep. Tremor of the fingers can be
Table 568-2  Major Symptoms and Signs of Hyperthyroidism and of Graves Disease and Conditions Associated with Graves Disease

### MANIFESTATIONS OF HYPERTHYROIDISM

**Signs**
- Sinus tachycardia, atrial fibrillation (rare in children), supraventricular tachycardia
- Fine tremor, hyperkinesia, hyperreflexia
- Warm, moist skin
- Palmar erythema, onycholysis
- Hair loss or thinning
- Osteoporosis
- Muscle weakness and wasting
- High-output heart failure
- Chorea
- Periodic (hypokalemic) paralysis (primarily in Asian men)
- Psychosis (rare)

**Symptoms**
- Hyperactivity, irritability, altered mood, insomnia, anxiety, poor concentration
- Heat intolerance, increased sweating
- Palpitations
- Fatigue, weakness
- Dyspnea
- Weight loss with increased appetite (weight gain in 10% of patients)
- Pruritus
- Increased stool frequency
- Thirst and polyuria
- Oligomenorrhea or amenorrhea

### MANIFESTATIONS OF GRAVES DISEASE

**Diffuse goiter**

**Ophthalmopathy**

A feeling of grittiness and discomfort in the eye

Retrobulbar pressure or pain

Eyelid lag or retraction

Periorbital edema, chemosis, scleral or conjunctival injection

Exophthalmos (proptosis)

Extraocular muscle dysfunction

Exposure keratitis

Optic neuropathy

Localized dermopathy (rare in children)

Lymphoid hyperplasia

Thyroid acropachy (rare in children)

### CONDITIONS ASSOCIATED WITH GRAVES DISEASE

- Type 1 diabetes mellitus
- Addison disease
- Vitiligo
- Pernicious anemia
- Alopecia areata
- Myasthenia gravis
- Celiac disease


noticed if the arm is extended. There may be a voracious appetite combined with loss of or no increase in weight. Recent height measurements might show acceleration in growth velocity.

The size of the thyroid is variable. It may be so minimally enlarged that it initially escapes detection, but with careful examination, a diffuse goiter, soft with a smooth surface, is found in almost all patients. Exophthalmos is noticeable in most patients but is usually mild. Lagging of the upper eyelid as the eye looks downward, impairment of convergence, and retraction of the upper eyelid and infrequent blinking may be present (Figs. 568-1 and 568-2). Ocular manifestations can produce pain, lid erythema, chemosis, decreased extraocular muscle function, and decreased visual acuity (corneal or optic nerve involvement). The skin is smooth and flushed, with excessive sweating. Muscular weakness is uncommon but may be severe enough to result in clumsiness. Tachycardia, palpitations, dyspnea, and cardiac enlargement and insufficiency cause discomfort but rarely endanger the patient’s life. Atrial fibrillation is a rare complication. Mitral regurgitation, probably resulting from papillary muscle dysfunction, is the cause of the apical systolic murmur present in some patients. The systolic blood pressure and the pulse pressure are increased. Reflexes are brisk, especially the return phase of the Achilles reflex. Many of the findings in Graves disease result from hyperactivity of the sympathetic nervous system.

**Thyroid crisis, or thyroid storm,** is a form of hyperthyroidism manifested by a severe biochemical derangement, acute onset, hyperthermia, tachycardia, heart failure, and restlessness. There may be rapid progression to delirium, coma, and death. Precipitating events include trauma, infection, radioactive iodine treatment, or surgery. **Apathetic**
(or masked) hyperthyroidism is another variety of hyperthyroidism characterized by extreme listlessness, apathy, and cachexia. A combination of both forms can occur. These symptom complexes are rare in children.

**LABORATORY FINDINGS**

Levels of TSH are suppressed to below the lower range of normal. Serum levels of T₄, T₃, free T₄, and free T₃ are typically elevated. In some patients, levels of T₄ may be more elevated than those of T₃. Antithyroid antibodies, including thyroid peroxidase antibodies, are often present. Most patients with newly diagnosed Graves disease have measurable TRSAb; the 2 methods to measure TRSAb are thyroid-stimulating immunoglobulin or thyrotropin-binding inhibitory immunoglobulin. Measurement of thyroid-stimulating immunoglobulin or thyrotropin-binding inhibitory immunoglobulin is useful in confirming the diagnosis of Graves disease. Children who experience an acceleration of growth might also have advanced skeletal maturation. Bone density may be reduced at diagnosis but returns to normal with treatment.

**DIFFERENTIAL DIAGNOSIS**

Diagnosis is rarely difficult once hyperthyroidism is considered. Elevated levels of T₄ or free T₃ and TSH in association with suppressed levels of TSH are usually diagnostic (see Table 568-1). The combination of diffuse goiter and prolonged hyperthyroidism is nearly always caused by Graves disease, and the presence of characteristic eye or skin changes is diagnostic. Documentation of elevated TRSAb can confirm the diagnosis.

Other causes of hyperthyroidism are uncommon. In rare cases where clinical assessment cannot distinguish Graves hyperthyroidism from painless sporadic thyroiditis, ¹²³I radioiodine uptake can be measured and used to determine the appropriateness of antithyroid medication. If a discrete thyroid nodule is palpated, a ¹²³I scan should be performed to assess the possibility of a hyperfunctioning nodule(s). Some children with toxic multinodular goiter may have either a TSH receptor–activating mutation or McCune-Albright syndrome.

When hyperthyroxinemia is caused by exogenous thyroid hormone (thyrotoxicosis factitia), levels of free T₄ and TSH are the same as those seen in Graves disease but, in contrast to Graves hyperthyroidism, serum thyroglobulin is very low, thyroid size is small, and ¹²³I radioiodine uptake is suppressed.

**TREATMENT**

Most pediatric endocrinologists recommend initial medical therapy using antithyroid drugs rather than radioiodine or subtotal thyroidectomy, although radioiodine is gaining acceptance as initial treatment in children older than 10 yr of age. All therapeutic options have advantages and disadvantages (Table 568-3). The 2 antithyroid drugs used historically are propylthiouracil and methimazole (Tapazole). Both compounds inhibit incorporation of trapped inorganic iodide into organic compounds. However, there are important differences between the drugs. Methimazole is at least 10 times more potent than propylthiouracil on a weight basis and has a much longer serum half-life (6-8 hr vs 0.5 hr); propylthiouracil generally is administered 3 times daily, but methimazole can be given once daily. Unlike methimazole, propylthiouracil is heavily protein bound and has a lesser ability to cross the placenta and to pass into breast milk; theoretically, therefore, propylthiouracil is the preferred drug during pregnancy and for nursing mothers. Because of reports of severe liver disease in patients treated with propylthiouracil, with some patients requiring liver transplant or potentially suffering a fatal outcome, the consensus is to use only methimazole to treat children with Graves disease.

Adverse reactions occur with antithyroid drugs; most are mild, but some are life-threatening. Minor adverse effects occur in approximately 10-20%, and more-severe adverse effects occur in 2-5% of children. Reactions are unpredictable and can occur after therapy of any duration. Transient granulocytopenia (<2,000/mm³) is common; it is asymptomatic and is not a harbinger of agranulocytosis, and it usually is not a reason to discontinue treatment. Transient urticarial rashes are common. They may be managed by a short period off therapy, and then restarting the antithyroid drug. The most severe reactions are hypersensitive and include agranulocytosis (0.1-0.5%), hepatitis (0.2-1.0%), a lupus-like polyarthritis syndrome, glomerulonephritis, and an antineutrophilic cytoplasmic antibody–positive vasculitis involving the skin and other organs. Severe liver disease, including liver failure requiring transplantation, have been reported exclusively.

| **Table 568-3** Treatments for Hyperthyroidism Caused by Graves Disease |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **TREATMENT**               | **ADVANTAGE**               | **DISADVANTAGE**            | **COMMENT**                 |
| Antithyroid drugs           | Noninvasive                 | Cure rate 30-80% (average: 40-50%) | First-line treatment in children and adolescents and in pregnancy |
|                            | Less initial cost           | Adverse drug reactions       | Initial treatment in severe cases or preoperative preparation |
|                            | Low risk of permanent hypothyroidism | Drug compliance required | |
|                            | Possible remission          |                            |                               |
| Radioactive iodine (¹²³I)   | Cure of hyperthyroidism     | Permanent hypothyroidism is almost inevitable | No evidence for infertility, birth defects, cancer when currently recommended doses are applied |
|                            | Most cost-effective         | Might worsen ophthalmopathy | |
|                            |                            | Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism | |
| Surgery                    | Rapid, effective treatment especially in patients with large goiter | Most invasive therapy | Potential use in pregnancy if major side effect from antithyroid drugs |
|                            |                            | Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) | Useful when coexisting suspicious nodule is present or thyromegaly is massive |
|                            |                            | Most costly therapy         | Option for patients who refuse radioiodine |
|                            |                            | Permanent hypothyroidism; pain; scarring | |

with propylthiouracil. The most common liver disease associated with methimazole is cholestatic jaundice, reversible when the drug is discontinued. Patients with severe adverse effects should be treated with radiiodine or thyroidectomy. In rare instances where hyperthyroidism is severe and methimazole cannot be used, a short course of propylthiouracil may be offered to restore euthyroidism prior to definitive therapy. Cases of congenital skin defects (aplasia cutis) have been seen in infants exposed in fetal life to methimazole, but this association does not appear to be a strong one.

The initial dosage of methimazole is 0.25-1.0 mg/kg/24 hr given once or twice daily. Smaller initial dosages should be used in early childhood. Careful surveillance is required after treatment is initiated. Rising serum levels of TSH to greater than normal indicates overtreatment and leads to increased size of the goiter. Clinical response becomes apparent in 3-6 wk, and adequate control is evident in 3-4 mo. The dose is decreased to the minimal level required to maintain a euthyroid state.

Most studies report a remission rate of approximately 25% after 2 yr of antithyroid drug treatment in children. Some studies find that longer treatment is associated with higher remission rates, with 1 study reporting a 50% remission rate after 4.5 yr of drug treatment. If a relapse occurs, it usually appears within 3 mo and almost always within 6 mo after therapy has been discontinued. Therapy may be resumed in case of relapse. Patients older than 13 yr of age, boys, those with a higher body mass index, and those with small goiters and modestly elevated T₃ levels appear to have earlier remissions.

A β-adrenergic blocking agent such as propranolol (0.5-2.0 mg/kg/24 hr orally, divided 3 times daily) or atenolol (1-2 mg/kg orally given once daily) is a useful supplement to antithyroid drugs in the management of severely toxic patients. Table 568-4 lists additional therapies for thyroid storm. Thyroid hormones potentiate the actions of catecholamines, including tachycardia, tremor, excessive sweating, lid lag, and stare. These symptoms abate with the use of propranolol, which does not, however, alter thyroid function or exophthalmos.

Radioiodine treatment or surgery is indicated when adequate cooperation for medical management is not possible, when an adequate trial of medical management has failed to result in permanent remission, or when severe side effects preclude further use of antithyroid drugs. Either of these treatments may also be preferred by the patient or parent.

### Table 568-4 Management of Thyroid Storm in Adolescents

<table>
<thead>
<tr>
<th>GOAL</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of thyroid hormone formation and secretion</td>
<td>Propylthiouracil, 400 mg every 8 hr PO or by nasogastric tube; saturated solution of potassium iodide, 3 drops every 8 hr</td>
</tr>
<tr>
<td>Sympathetic blockade</td>
<td>Propranolol, 20-40 mg every 4-6 hr or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>Prednisone 20 mg bid</td>
</tr>
<tr>
<td>Supportive therapy</td>
<td>Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins); temperature control (cooling blankets, acetaminophen; avoid salicylates) O₂ if required; digitalis for heart failure and to slow ventricular response; pentobarbital for sedation; treatment of precipitating event (e.g., infection)</td>
</tr>
</tbody>
</table>

Radiiodine is an effective therapy for Graves disease in children. In patients with severe thyrotoxicosis, euthyroidism should be restored with methimazole prior to radioablation in order to deplete the gland of preformed hormone and reduce the risk of thyrotoxic flare from radiation thyroiditis. If a patient is taking thionamides, they must be stopped 3-5 days before radioiodine administration to avoid inhibition of uptake. In children, the goal is to select a dose of radioiodine high enough to ensure complete ablation of thyroid tissue. Most centers obtain a diagnostic radioiodine uptake measurement before treatment and then use this to calculate a ¹³¹I dose that delivers an absorbed thyroid dose of >150 μCi/g. Alternatively, an empirical fixed ¹³¹I dose (usually 15 mCi) can be offered. The theoretical advantage of calculated doses is that they define for each individual patient the lowest administered dose that achieves the therapeutic target. This benefit is most important in small children, as the absorbed radiation dose to the bone marrow and other normal tissues is inversely proportional to body size. Based upon this concept and theoretical modeling of radiation exposure, current consensus guidelines recommend that ¹³¹I therapy be avoided in very small children who are younger than 5 yr of age and that administered doses in children between 5 and 10 yr of age be <10 mCi. As with other Graves therapies, ¹³¹I ablation has a low but obligate failure rate (5-20%). Patients with persistent hyperthyroidism more than 6 mo after their first ¹³¹I therapy can be offered retreatment.

**Thyroidectomy**, a safe procedure when performed by an experienced surgeon, is done only after the patient has been brought to a euthyroid state. This may be accomplished with methimazole over 2-3 mo. After a euthyroid state has been attained, a saturated solution of potassium iodide, 3-5 drops 3 times per day, is added to the regimen for 2 wk before surgery to decrease the vascularity of the gland. In expert hands, complications of surgical treatment are rare and include hypoparathyroidism (transient or permanent) and paralysis of the vocal cords. The incidence of residual or recurrent hyperthyroidism or hypothyroidism depends on the extent of the surgery. Most recommend near-total thyroidectomy. The incidence of recurrence is low, and most patients become hypothyroid. Referral to a surgeon with extensive experience in thyroidectomy and a low personal complication rate is paramount.

The **ophthalmopathy** usually remits gradually and independently of the hyperthyroidism. Severe ophthalmopathy can require treatment with high-dose prednisone, orbital radiotherapy (of questionable value), or orbital decompression surgery. Cigarette smoking is a risk factor for thyroid eye disease and should be avoided or discontinued to avoid progression of eye involvement.

*Bibliography is available at Expert Consult.*

### 568.2 Congenital Hyperthyroidism

**Stephen A. Huang and Stephen H. LaFranchi**

#### Etiology and Pathogenesis

Neonatal Graves disease is caused by transplacental passage of TRSAb, but the clinical onset, severity, and course may be modified by the concurrent presence of thyrotropin receptor–blocking antibody and by the transplacental passage of antithyroid drugs taken by the mother. Very high levels of TRSAb usually result in classic neonatal hyperthyroidism, but if the infant has been exposed to antithyroid drugs, onset of symptoms is delayed by 3-4 days as the maternally derived antithyroid drug is metabolized. If thyrotropin receptor–blocking antibody is also present, onset of hyperthyroid symptoms may be delayed for several weeks. The mothers of these infants have active Graves disease, Graves disease in remission, a past history of Graves disease managed by radioactive iodine ablation or surgery, or rarely hypothyroidism and a history of lymphocytic thyroiditis.

Neonatal hyperthyroidism occurs in only approximately 2% of infants born to mothers with a history of Graves disease. Fetal tachycardia and goiter can allow prenatal diagnosis and fetal ultrasound
Bibliography


Occasionally, neonatal hyperthyroidism does not remit but persists into childhood. These patients can have an impressive family history of hyperthyroidism. Neonatal hyperthyroidism, without evidence for autoimmune disease in mother or infant, may be caused by a mutation in the TSHR gene that produced constitutive activation of the receptor. Neonatal hyperthyroidism has also been reported in patients with McCune-Albright syndrome, a result of an activating mutation of the α subunit of the G-protein. Under these circumstances, hyperthyroidism recurs when antithyroid drugs are discontinued; these children eventually must be treated with radioiodine or surgery.

**PROGNOSIS**

Advanced osseous maturation, microcephaly, and cognitive impairment occur when treatment is delayed. Intellectual development is normal in most treated infants with neonatal Graves disease, though some manifest neurocognitive problems from in utero hyperthyroidism. In some infants, in utero hyperthyroidism appears to suppress the hypothalamic-pituitary-thyroid feedback mechanism, and they develop permanent central hypothyroidism, requiring lifelong thyroid hormone treatment.

Bibliography is available at Expert Consult.
Bibliography
Carcinoma of the Thyroid

Stephen A. Huang and Stephen H. LaFranchi

EPIDEMIOLOGY
Carcinoma of the thyroid is rare in childhood; the annual incidence in children younger than 15 yr of age is approximately 2 in 100,000 cases, compared with an annual incidence at all ages around the world of 4-10 in 100,000 cases. In the last 2 decades, the incidence in children has increased 2-fold. Compared to adults, childhood thyroid cancers are characterized by dramatically higher rates of metastasis and recurrence. Despite being widespread at discovery, pediatric thyroid cancers usually have an indolent course and, with adequate treatment, most patients have a favorable outcome.

PATHOGENESIS
At all ages, the vast majority of differentiated thyroid cancers are of follicular cell origin and, in North America, papillary carcinoma (88%) is the most common subtype. Interestingly, while their histologic features are similar, the thyroid cancers of childhood are genetically distinct from their adult counterparts. Although up to 70% of adults with papillary thyroid cancer exhibit pathogenic somatic mutations in BRAF or RAS, these mutations are extremely rare in children with papillary cancer. In contrast, RET-PTC translocations, which result in chimeric proteins containing the tyrosine kinase domains of RET fused to the regulatory sequences of ubiquitously expressed genes such as H1 and ELE1, are often found in childhood thyroid cancers. After papillary thyroid cancer, follicular cancer (10%) is the next most common type of childhood thyroid cancer. Medullary cancer (2%) and anaplastic thyroid cancers are relatively rare. Of note, only thyroid cancers of follicular cell origin (papillary and follicular carcinomas) respond to the adjunctive therapies of ¹³¹I therapy and thyroid-stimulating hormone (TSH) suppression.

Up to 10% of cases of follicular cell–derived thyroid cancers are familial, and these are usually inherited in an autosomal dominant manner. Familial syndromes associated with an increased risk of thyroid neoplasia include Cowden syndrome (characterized by mucocutaneous...
lesions, breast cancer, macrocephaly, and endometrial tumors) and familial adenomatous polyposis. Germline mutations in the DICER-1 gene have also been recognized as a cause of thyroid neoplasia. The evaluation of a child with thyroid nodule should include a medical and family history to assess for features of these syndromes.

The thyroid gland of children is unusually sensitive to exposure to external radiation. There probably is no threshold dose; 1 Gy results in a 7.7 relative risk of thyroid cancer. In the past, approximately 80% of children with cancer of the thyroid had received inappropriate therapeutic irradiation of the neck and adjacent areas during infancy for benign conditions such as “enlarged” thymus, hypertrophied tonsils and adenoids, hemangiomas, nevi, eczema, tinea capitis, and “cervical adenitis.” With the discontinuation of irradiation for benign conditions, this cause of thyroid cancer has vanished. The long-term survival of children who have received appropriate therapeutic irradiation of areas of the neck for neoplastic disease has made this cause of thyroid cancer and nodules increasingly prevalent; increased dose, younger age at time of treatment, and female sex are factors that increase the risk of thyroid cancer. Long-term risk data for cancer are sparse, but 15-50% of children who have received irradiation and chemotherapy for Hodgkin disease, leukemia, bone marrow transplantation, brain tumors, and other malignancies of the head and neck have elevated levels of TSH within the 1st yr of therapy, and 5-20% progress to hypothyroidism during the next 5-7 yr. Most large groups of treated children have a 10-30% incidence of benign thyroid nodules and an increased incidence of thyroid cancer. The latter begins to appear within 3-5 yr after radiation treatment and reaches a peak in 15-25 yr. It is unknown whether there is a period after which no more tumors develop. Administration of 131I for diagnostic or therapeutic purposes does not appear to increase the risk of thyroid cancer.

Thyroid cancer has been reported in children with congenital goiter or ectopic thyroid tissue. In these patients, and also in children with autoimmune thyroiditis and hypothyroidism, chronic TSH stimulation appears to play a pathogenic role. It is unclear if the course of thyroid cancer differs in these patients compared to the general population. From a practical standpoint, nodules that are detected in the context of these disorders should be fully evaluated for cancer risk as in other children.

**CLINICAL MANIFESTATIONS**

The incidence of childhood thyroid cancer peaks in adolescence and girls are more commonly affected than boys. A painless nodule in the thyroid or in the neck is the usual presentation of disease. Rapid growth and large nodule size, firmness, fixation to adjacent tissues, hoarseness, dysphagia, and neck lymphadenopathy should heighten the concern for thyroid cancer. Cervical lymph node metastasis is common, so any unexplained cervical lymph node enlargement warrants examination of the thyroid. The lungs are the most common site of distant metastasis. There may be no clinical manifestations referable to them and formal pulmonary function testing may be normal even with widespread macroscopic metastases. Radiologically, they appear as diffuse miliary or nodular infiltrations, typically greatest in the posterior basal portions. They may be mistaken for tuberculosis, histoplasmosis, or sarcoidosis. Other sites of metastasis include the mediastinum, axilla, long bones, skull, and brain. Almost all children are euthyroid, but rarely, the carcinoma is functional and produces symptoms of hyperthyroidism.

**DIAGNOSIS**

As detailed in the following section, patients usually present with a neck mass and virtually all have a thyroid nodule of significant size upon ultrasound. While several imaging features are significantly associated with thyroid cancer risk, none have sufficient negative predictive value to forgo tissue diagnosis. Papillary thyroid cancer is characterized by nuclear abnormalities that are well identified by cytology and fine-needle aspiration is the gold standard in the evaluation of adults with nodules. Growing literature supports its use in the pediatric population. In most cases, operative pathology is required to confirm the diagnosis of thyroid cancer and to stage the extent of disease.

**TREATMENT**

The primary therapy for thyroid cancer is surgical resection. Because intrathyroidal spread is common in papillary thyroid, near-total thyroidectomy is the favored approach. Prior to this surgery, neck ultrasonography should be performed to screen for sonographically abnormal lymph nodes. Suspicious lymph nodes may be biopsied preoperatively to determine the appropriateness and extent of initial lymph node dissection.

With the exception of very-low-risk patients, thyroidectomy is usually followed by adjunctive therapy with both TSH suppression (dosing levothyroxine to lower serum TSH and deprive residual thyroid cancer cells of this growth factor) and 131I therapy (to ablate the normal thyroid remnant and/or to treat residual thyroid cancer).

**PROGNOSIS**

Although extrathyroidal invasion and distant metastasis are more common in the pediatric population, most children with thyroid cancer have a good outcome. Families should be counseled that the response to 131I therapy is slow and that repeated treatments and years of care may be required to eliminate the disease. They should further be informed that many patients who are unable to achieve complete cure can be maintained in the well state with stable or slowly progressive cancer burden. For rare children with aggressive cancers that progress despite the optimization of conventional therapies, newer options, such as oral tyrosine kinase inhibitors, are available through research trials or on a compassionate basis. As with any cancer, psychosocial supports must be available, including access to social work and other mental health professionals.

Among solid tumors, thyroid cancer is unique in its capacity for late recurrence, sometimes occurring decades after initial presentation. For this reason, all children with thyroid cancer deserve lifelong monitoring for disease progression. For most patients, serum thyroglobulin is a sensitive and specific cancer marker. However, it must be recognized that about one fourth of patients have circulating antithyroglobulin autoantibodies that interfere with standard thyroglobulin assays and produce artifactualy low measurements. Because of this, antithyroglobulin autoantibodies must always be measured whenever serum thyroglobulin is assayed to confirm the latter’s reliability. As most thyroid cancer recurrences are local, surveillance should include serial neck ultrasounds. Patients with higher recurrence risk or documentation of distant metastases typically benefit from additional anatomic imaging studies and from extended surveillance studies performed during TSH stimulation.

**Bibliography is available at Expert Consult.**

569.1 Solitary Thyroid Nodule

Stephen A. Huang and Stephen H. LaFranchi

The frequency of thyroid nodules increases with age. While sonographically detectable nodules are present in 19-67% of randomly selected adults, the estimated frequency of nodules in children is only 0.05-2.0%. Although early pediatric series cited extremely high rates of cancer in thyroid nodules (up to 70%), more recent studies of children report lower cancer prevalence (around 20-26%) that is similar to the 5-15% prevalence observed in adults. Thus, when a thyroid nodule is discovered in a child, parents should be counseled that the majority of nodules are benign.

Benign disorders that can occur as a solitary thyroid mass include benign adenomatous or colloid nodules, as well as a variety of congenital cysts (Table 569-1). A suddenly appearing or rapidly enlarging thyroid mass can indicate hemorrhage into a cyst or benign adenoma. When evaluating a child with a thyroid nodule, it is helpful to begin by measuring serum TSH.

In rare patients who present with a suppressed serum TSH, a thyroid scan, preferably using 131I or 123I-TC-perchlorate, should be performed to assess the possibility of a benign hyperfunctioning thyroid nodule. All other patients should proceed directly to ultrasound and, if a
Bibliography


Medullary thyroid carcinoma (MTC) arises from the parafollicular cells (C cells) of the thyroid and accounts for approximately 2% of thyroid malignancies in children. The majority of MTC cases are sporadic, but approximately 25% are familial, autosomal dominant disorders. Hereditary MTC is divided into 3 distinct syndromes: multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), and familial MTC. In contrast to the somatic mutations associated with sporadic MTC, germline mutations in the RET protooncogene on chromosome 10q11.2 are inheritable and can cause familial medullary thyroid cancer. Once an index case is diagnosed in a family, it is important to pinpoint the specific RET mutation and then genotype all 1st-degree relatives for the mutation. Many RET mutations have been well studied and strong genotype–phenotype associations have been established to predict disease aggressiveness. In carriers, thyroidectomy before the MTC has spread outside the gland represents the best chance for a cure and the patient’s specific genotype can be used to guide the timing of prophylactic surgery.

The most common presentation of sporadic MTC is an asymptomatic, palpable thyroid nodule. When the tumor occurs sporadically, it is usually unifocal, but in the familial form, it is usually multicentric, and it begins as hyperplasia of parafollicular cells. The diagnosis of MTC can often be made through routine FNA cytology, but documentation of high calcitonin in an FNA washing or in the patients’ serum is helpful as confirmation. The diagnosis of MTC warrants genetic testing for RET mutation and screens for MEN2-associated pheochromocytoma and hyperparathyroidism should be obtained prior to anesthesia for thyroidectomy. No clinically recognizable manifestations result from the elevated serum levels of calcitonin or CEA. Nonetheless, these tests are helpful in screening and monitoring therapy.

**MULTIPLE ENDOCRINE NEOPLASIA, TYPE 2A**
MEN2A is an autosomal dominant disorder characterized by MTC, pheochromocytoma, and parathyroid hyperplasia. At least 19 different specific missense mutations of exon 10 or 11 of the extracellular domain of the RET gene have been described for MEN2A and for cases of familial MTC. DNA analysis permits unambiguous identification of carriers of the RET protooncogene mutation. Penetration of MTC is close to 100%, but there is much variability in the other manifestations of MEN2A. C-cell hyperplasia or MTC usually appears earlier than pheochromocytoma. Pheochromocytomas are often bilateral and may be multiple. Adrenal medullary hyperplasia is known to precede pheochromocytoma, but the detectable latent period is short. Hypercalcemia is a late manifestation and indicates hyperparathyroidism. The parathyroid glands might reveal chief-cell hyperplasia or only hypercellularity.

**MULTIPLE ENDOCRINE NEOPLASIA, TYPE 2B**
MEN2B is an autosomal dominant disorder characterized by MTC and pheochromocytomas but not hyperparathyroidism. The distinguishing feature of MEN2B, also called the mucosal neuroma syndrome, is the occurrence of multiple neuromas and a characteristic phenotype that includes Marfan-like facies. A missense mutation of the RET protooncogene in exon 16, the tyrosine catalytic domain of RET, is found in 93% of families; all patients have had the same point mutation. The neuromas most often occur on the tongue, buccal mucosa, lips, and conjunctivae. Peripheral neurofibromas and café-au-lait patches may be present, and intestinal ganglioneuromatosis is common. Diffuse proliferation of nerves and ganglion cells is found in mucosal, submucosal, myenteric, and subserosal plexus involving the small and large bowel as well as the esophagus. The patients may be tall, with arachnodactyly and a Marfan-like appearance. Scilosis, pectus excavum, pes cavus, and muscular hypotonia are common. The eyelids may be thickened and everted, the lips patulous and blubbery, the jaw prognathic. Feeding difficulties, poor sucking, diarrhea, constipation, and failure to thrive can begin in infancy or early childhood, many years before the appearance of neuromas or endocrine symptoms.

**TREATMENT**
Total thyroidectomy is indicated for all children who are shown by genetic studies to carry high-risk RET mutations. Recognition of familial forms of this tumor is critical to the early diagnosis and intervention in children at risk. MTC develops at an earlier age in patients with MEN2B and is more aggressive than in MEN2A. MTC has been seen in a 6 mo old child with MEN2B and in a 3 yr old child with MEN2A. In MEN2A, there is genotype–phenotype correlation between the specific mutation and the onset of C-cell hyperplasia or MTC. With codon 634 mutations, MTC occurs at an early age, whereas with mutations at codons 618, 620, and 804, MTC tends to occur at a later age. In young children, recommendations for the timing of prophylactic thyroidectomy are available for the common RET mutations. All these children should be screened for pheochromocytoma before surgery. Monitoring the serum levels of calcitonin and carcinoembryonic antigen is useful in following the course of the disease after operation and in detecting metastatic lesions. Periodic screening for the development of pheochromocytoma and hyperparathyroidism is indicated. Metastases to the regional lymph nodes and to the liver can occur. Early clinic studies support that prophylactic thyroidectomy is effective in preventing death from MTC.

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**Bibliography**


Bibliography


The occurrence of these fragments in serum has led to the development of a variety of assays. The 1-34 aminoterminal (N-terminus) fragments possess biologic activity and are present in low amounts in the circulation; assay of these fragments is most useful for detecting acute secretory changes. The carboxyterminal (C-terminus) and midregion fragments, although biologically inert, are cleared more slowly from the circulation and represent 80% of plasma immunoreactive PTH; concentrations of the C-terminal fragment are 50-500 times the level of the active hormone. The C-terminal assays are effective in detecting hyperparathyroidism, but because C-terminal fragments are removed from the circulation by glomerular filtration, these assays are less useful for evaluating the secondary hyperparathyroidism characteristic of renal disease. Only certain sensitive radioimmunoassays for PTH can differentiate the subnormal concentrations that occur in hyperparathyroidism from normal levels.

When serum levels of calcium fall, the signal is transduced through the calcium-sensing receptor, and secretion of PTH increases (Fig. 570-1). PTH stimulates activity of 1α-hydroxylase in the kidney, enhancing production of 1,25-dihydroxycholecalciferol, also written 1,25(OH)2D3. The increased level of 1,25(OH)2D3 induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa, with resultant absorption of calcium. PTH also mobilizes calcium by directly enhancing bone resorption, an effect that requires 1,25(OH)2D3. The effects of PTH on bone and kidney are mediated through binding to specific receptors on the membranes of target cells and through activation of a transduction pathway involving a G-protein coupled to the adenylate cyclase system (see Chapter 572).

The calcium-sensing receptor regulates the secretion of PTH and the reabsorption of calcium by the renal tubules in response to alterations in serum calcium concentrations. The gene for the receptor is located on chromosome 3q13.3-q21 and encodes a cell surface protein that is expressed in parathyroid glands and kidneys and belongs to the family of G-protein–coupled receptors. In the normally functioning calcium-sensing receptor, hypocalcemia induces increased secretion of PTH and hypercalcemia depresses PTH secretion. Loss-of-function mutations cause an increased set point with respect to serum calcium, resulting in hypercalcemia and in the conditions of familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Acquired hypocalciuric hypercalcemia may be a result of autoantibodies to the calcium-sensing receptor and manifests with hypercalcemia and hyperparathyroidism. Gain-of-function mutations result in depressed secretion of PTH in response to hypocalcemia, leading to the syndrome of familial hypocalciuria with hypercalcemia (see Fig. 570-1).

### PARATHYROID HORMONE–RELATED PEPTIDE

PTHrP is homologous to PTH only in the first 13 amino acids of its amino terminus, 8 of which are identical to PTH. Its gene is on the short arm of chromosome 12 and that of PTH is on the short arm of chromosome 11.

PTHrP, like PTH, activates PTH receptors in kidney and bone cells and increases urinary cyclic adenosine monophosphate and renal production of 1,25(OH)2D3. It is produced in almost every type of cell of the body, including every tissue of the embryo at some stage of development. PTHrP is critical for normal fetal development. Inactivating mutations of the receptor for PTH/PTHrP result in a lethal bone disorder characterized by short limbs and markedly advanced bone maturation known as Blomstrand chondrodysplasia (see Fig. 570-1). PTHrP appears to have a paracrine or autocrine role because serum levels are low except in a few clinical situations. Cord blood contains levels of PTHrP that are 3-fold higher than in serum from adults; it is produced by the fetal parathyroid glands and appears to be the main agent stimulating maternal-fetal calcium transfer. PTHrP appears to be essential for normal skeletal maturation of the fetus, which requires 30 g of calcium during a normal gestation. During pregnancy, maternal absorption of calcium increases from about 150 mg daily to 400 mg during the 2nd trimester.

As in cord blood, PTHrP levels are increased during lactation and in patients with benign breast hypertrophy. Breast milk and pasteurized bovine milk have levels of PTHrP that are 10,000 times higher than those of normal plasma. Most instances of the hormonal hypercalcemia syndrome of malignancy are caused by elevated concentrations of PTHrP.

### VITAMIN D

See Chapter 51.

### CALCITONIN

Calcitonin is a 32-amino-acid polypeptide. Its gene is on chromosome 11p and is tightly linked to that of PTH. The gene for calcitonin encodes 3 peptides: calcitonin, a 21-amino-acid carboxyterminal flanking peptide (katalcalcin), and a calcitonin gene–related peptide. Katalcalcin and calcitonin are cosecreted in equimolar amounts by the parafollicular cells (C cells) of the thyroid gland. Calcitonin appears to be of little consequence in children and adults because very high levels in patients with medullary carcinoma of the thyroid (a tumor arising from the C cells) do not cause hypercalcemia. In the fetus, however, circulating levels are high and appear to augment bone metabolism and skeletal growth; these high levels are probably stimulated by the normally high fetal calcium levels. Unlike the high levels in cord blood and circulating concentrations in young children, levels in older children and adults are low. Infants and children with congenital hypothyroidism (and presumed deficiency of C cells) have lower levels of calcitonin than do normal children.

Its action appears to be independent of PTH and vitamin D. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts. This action of calcitonin is the rationale for its use in treatment of Paget disease. Calcitonin is synthesized in other organs, such as the gastrointestinal tract, pancreas, brain, and pituitary. In these organs, calcitonin is thought to behave as a neurotransmitter to impose a local inhibitory effect on cell function.

### Bibliography

Available at Expert Consult.
**Bibliography**
CaSR and PTH/PTHrP-receptor mediate their effects through G protein-coupled signaling pathways, which in turn activate the adenyl cyclase (AC) and phospholipase C (PLC) systems. 

CaSR and PTH/PTHrP-receptor mediate their effects through G protein-coupled signaling pathways, which in turn activate the adenyl cyclase (AC) and phospholipase C (PLC) systems. 

Gq = G-pertussis-toxin-insensitive protein; Gi = G inhibitory protein; PIP2 = phosphatidyl inositol 4,5-bisphosphate; IP3 = inositol 1,4,5-triphosphate; DAG = diacylglycerol; PKC = protein kinase C.

Disorders due to PTH deficiency.
†Defect due to defect in the PTH/PTHrP receptor.
‡Defect due to insensitivity to PTH caused by defects downstream of the PTH/PTHrP receptor.
§Defect due to altered set point in the Ca++/PTH axis, associated with a gain-of-function mutation of the CaSR.

MELAS = mitochondrial encephalopathy, stroke-like episodes, and lactic acidosis.
KSS = Kearns Sayre syndrome (progressive external ophthalmoplegia, pigmentary retinopathy, heart block, and cardiomyopathy).
MTPDS = mitochondrial trifunctional protein deficiency syndrome.
HDR = hypoparathyroidism, deafness, and renal anomalies.
APECED = autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy.

Figure 570-1 Some components involved in calcium homeostasis. The calcium-sensing receptor (CaSR) and PTH/PTHrP receptor mediate their effects through G-protein–coupled signaling pathways, which, in turn, activate the adenyl cyclase (AC) and phospholipase C (PLC) systems. (From Thakker RV: Genetic development in hypoparathyroidism, Lancet 357:974–976, 2001.)
ETIOLOGY
Hypocalcemia is common in neonates between 12 and 72 hr of life, especially in premature infants, in infants with asphyxia, and in infants of diabetic mothers (early neonatal hypocalcemia; see Chapter 106; Table 571-1 and Fig. 571-1). After the 2nd to 3rd day and during the 1st wk of life, the type of feeding also is a determinant of the level of serum calcium (late neonatal hypocalcemia). The role played by the parathyroid glands in these hypocalcemic infants remains to be clarified, although functional immaturity of the parathyroid glands is invoked as 1 pathogenetic factor. In a group of infants with transient idiopathic hypocalcemia (1-8 wk of age), serum levels of parathyroid hormone (PTH) are significantly lower than those in normal infants. It is possible that the functional immaturity is a manifestation of a delay in development of the enzymes that convert glandular PTH to secreted PTH; other mechanisms are possible.

APLASIA OR HYPOPLASIA OF THE PARATHYROID GLANDS
Aplasia or hypoplasia of the parathyroid glands is often associated with the DiGeorge/velocardiofacial syndrome (see Fig. 570-1). This syndrome occurs in 1 in 4,000 newborns. In 90% of patients, the condition is caused by a deletion of chromosome 22q11.2. Approximately 25%

<table>
<thead>
<tr>
<th>Chapter 571</th>
<th>Hypoparathyroidism</th>
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<tbody>
<tr>
<td><strong>Daniel A. Doyle</strong></td>
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**Table 571-1 Causes of Hypocalcemia**

<table>
<thead>
<tr>
<th>I. Neonatal Disorders</th>
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<tbody>
<tr>
<td>A. Maternal Disorders</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Vitamin D deficiency</td>
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<td>High intake of alkali or magnesium sulfate</td>
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<td>Use of anticonvulsants</td>
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<td>Hyperparathyroidism</td>
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<td>B. Neonatal Disorders</td>
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<td>b. DiGeorge syndrome (TBX1)</td>
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<td>c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD); Kenny-Caffey syndrome 1 (short stature, medullary stenosis) (TBCE)</td>
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<td>d. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) (GATA3)</td>
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<td>f. Mitochondrial fatty acid disorders (Kearns-Sayre, Pearson, MELAS)</td>
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<td>3. Insensitivity to PTH</td>
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<td>d. Hypomagnesemia</td>
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</table>

HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episode; PTH, parathyroid hormone.

of these patients inherit the chromosomal abnormality from a parent. Neonatal hypocalcemia occurs in 60% of affected patients, but it is transitory in the majority; hypocalcemia can recur or can have its onset later in life. Associated abnormalities of the third and fourth pharyngeal pouches are common; these include conotruncal defects of the heart in 25%, velopharyngeal insufficiency in 32%, cleft palate in 9%, renal anomalies in 35%, and aplasia of the thymus with severe immune deficiency in 1%. This syndrome has also been reported in a small number of patients with a deletion of chromosome 10p13, in infants of diabetic mothers, and in infants born to mothers treated with retinoic acid for acne early in pregnancy.

X-LINKED RECESSIVE HYPOPARATHYROIDISM
Familial clusters of hypoparathyroidism with various patterns of transmission have been described. In 2 large North American pedigrees, this disorder appears to be transmitted by an X-linked recessive gene located on Xq26-q27. In these families, the onset of febrile seizures characteristically occurs in infants from 2 wk to 6 mo of age. The absence of parathyroid tissue after detailed examination of a boy with this condition suggests a defect in embryogenesis.

AUTOSOMAL RECESSIVE HYPOPARATHYROIDISM WITH DYSMORPHIC FEATURES
Autosomal recessive hypoparathyroidism with dysmorphic features has been described in Middle Eastern children. Parental consanguinity occurred for almost all of several dozen affected patients. Profound hypocalcemia occurs early in life, and dysmorphic features include microcephaly, deep-set eyes, beaked nose, micrognathia, and large floppy ears. Intraterine and postnatal growth restriction are severe, and cognitive impairment is common. The putative gene is on chromosome 1q42-43. The autosomal recessive form of hypoparathyroidism that occurs with type I polyglanular autoimmune disease is described subsequently. In a few patients with autosomal recessive inheritance of isolated hypoparathyroidism, mutations of the PTH gene have been found.

HYPOPARATHYROIDISM, SENSORINEURAL DEAFNESS, AND RENAL ANOMALY SYNDROME
Hypoparathyroidism, sensorineural deafness, and renal anomaly occur owing to mutations of the GATA3 gene. The protein encoded by this gene is essential in the development of the parathyroids, auditory system, and kidneys. The GATA3 gene is located at chromosome 10p14 and is nonoverlapping with the DiGeorge critical region at 10p13 (see Fig. 570-1).

SUPPRESSION OF NEONATAL PARATHYROID HORMONE SECRETION BECAUSE OF MATERNAL HYPERPARATHYROIDISM
Neonatal PTH secretion can be suppressed by maternal hyperparathyroidism, resulting in transient hypocalcemia in the newborn infant. It appears that neonatal hypocalcemia results from suppression of the fetal parathyroid glands by exposure to elevated levels of calcium in maternal and hence fetal serum. Tetany usually develops within 3 wk but may be delayed by 1 mo or more if the infant is breastfed. Hypocalcemia can persist for weeks or months. When the cause of hypocalcemia in an infant is unknown, measurements of calcium, phosphorus, and PTH should be obtained from the mother. Most affected mothers are asymptomatic, and the cause of their hyperparathyroidism is usually a parathyroid adenoma.

AUTOSOMAL DOMINANT HYPOPARATHYROIDISM
Patients with autosomal dominant hypoparathyroidism have an activating (gain-of-function) mutation of the Ca2+-sensing receptor, forcing the receptor to an "on" state with subsequent depression of PTH secretion even during hypocalcemia. The patients have hypercal-
ciuria. The hypocalcemia is usually mild and might not require treatment beyond childhood (see Fig. 570-1).

**HYPOPARATHYROIDISM ASSOCIATED WITH MITOCHONDRIAL DISORDERS**

Mitochondrial DNA mutations in Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome, and in mitochondrial trifunctional protein–deficiency syndrome are associated with hypoparathyroidism. A diagnosis of mitochondrial cytopathy should be considered in patients with unexplained symptoms, such as ophthalmoplegia, sensorineural hearing loss, cardiac conduction disturbances, and tetany (see Fig. 570-1).

**SURGICAL HYPOPARATHYROIDISM**

Removal or damage of the parathyroid glands can complicate thyroidectomy. Hypoparathyroidism has developed even when the parathyroid glands have been identified and left undisturbed at the time of operation. This may be the result of interference with the blood supply or of postoperative edema and fibrosis. Symptoms of tetany can occur abruptly postoperatively and may be temporary or permanent. In some instances, symptoms develop insidiously and go undetected until months after thyroidectomy. Occasionally, the first evidence of surgical hypoparathyroidism may be the development of cataract. The status of parathyroid function should be carefully monitored in all patients undergoing thyroidectomy.

Deposition of iron pigment or of copper in the parathyroid glands (thalassemia, Wilson disease) can produce hypoparathyroidism.

**AUTOIMMUNE HYPOPARATHYROIDISM**

An autoimmune mechanism for hypoparathyroidism is strongly suggested by the finding of parathyroid antibodies and by its frequent association with other autoimmune disorders or organ-specific antibodies. Autoimmune hypoparathyroidism is often associated with Addison disease and chronic mucocutaneous candidiasis. The association of at least 2 of these 3 conditions has been tentatively classified as autoimmune polyglandular disease type I. It is also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED). This syndrome is inherited in an autosomal recessive fashion and is not related to any single human leukocyte antigen–associated haplotype. One third of patients with this syndrome have all 3 components; 66% have only 2 of 3 conditions. The candidiasis almost always precedes the other disorders (70% of cases occur in children younger than 5 yr of age); the hypoparathyroidism (90% of cases occur after 3 yr of age) usually occurs before Addison disease (90% of cases occur after 6 yr of age). A variety of other disorders, including alopecia areata or totalis, malabsorption disorder, pernicious anemia, anemia, gonadal failure, chronic active hepatitis, vitiligo, and insulin-dependent diabetes, occurs at various times. Some of these associations might not appear until adult life. Autoimmune thyroid disease is a rare concomitant finding.

Affected siblings can have the same or different constellations of disorders (hypoparathyroidism, Addison disease). The disorder is exceptionally prevalent among Finns and Iranian Jews. The gene for this disorder is designated AIRE (autoimmune regulator); it is located on chromosome 21q22. It appears to be a transcription factor that plays an essential role in the development of immunologic tolerance. Patients with Addison disease as part of polyendocrinopathy syndrome type I have demonstrated adrenal-specific autoantibody reactivity directed against the side-chain cleavage enzyme.

**IDIOPATHIC HYPOPARATHYROIDISM**

The term idiopathic hypoparathyroidism should be reserved for the small residuum of children with hypoparathyroidism for whom no causative mechanism can be defined. Most children in whom onset of hypoparathyroidism occurs after the 1st few yr of life have an autoimmune condition. Autoantibodies to the extracellular domain of the calcium-sensing receptor have been identified in some patients with acquired hypoparathyroidism. One should always consider incomplete forms of DiGeorge syndrome or an activating calcium-sensing receptor mutation in the differential diagnosis.

**Clinical Manifestations**

There is a spectrum of parathyroid deficiencies with clinical manifestations varying from no symptoms to those of complete and longstanding deficiency. Mild deficiency may be revealed only by appropriate laboratory studies. Muscular pain and cramps are early manifestations; they progress to numbness, stiffness, and tingling of the hands and feet. There may be only a positive Chvostek or Trousseau sign or laryngeal and carpopedal spams. Convulsions with or without loss of consciousness can occur at intervals of days, weeks, or months. These episodes can begin with abdominal pain, followed by tonic rigidity, retraction of the head, and cyanosis. Hypoparathyroidism is often mistaken for epilepsy. Headache, vomiting, increased intracranial pressure, and papilledema may be associated with convulsions and might suggest a brain tumor.

In patients with long-standing hypocalcemia, the teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. The skin may be dry and scaly, and the nails might have horizontal lines. Mucocutaneous candidiasis, when present, antedates the development of hypoparathyroidism; the candidal infection most often involves the nails, the oral mucosa, the angles of the mouth, and less often, the skin; it is difficult to treat.

Cataracts in patients with long-standing untreated disease are a direct consequence of hypoparathyroidism; other autoimmune ocular disorders such as keratoconjunctivitis can also occur. Manifestations of Addison disease, lymphocytic thyroiditis, pernicious anemia, alopecia areata or totalis, hepatitis, and primary gonadal insufficiency may also be associated with those of hypoparathyroidism.

Permanent physical and mental deterioration occurs if initiation of treatment is long delayed.

**Laboratory Findings**

The serum calcium level is low (5-7 mg/dL), and the phosphorus level is elevated (7-12 mg/dL). Blood levels of ionized calcium (usually approximately 45% of the total) more nearly reflect physiologic adequacy but also are low. The serum level of alkaline phosphatase is normal or low, and the level of 1,25(OH)2D3 is usually low, but high levels have been found in some children with severe hypocalcemia. The level of magnesium is normal but should always be checked in hypocalcemic patients. Levels of PTH are low when measured by immunometric assay. Radiographs of the bones occasionally reveal an increased density limited to the metaphyses, suggesting heavy metal poisoning, or an increased density of the lamina dura. Radiographs or CT scans of the skull can reveal calcifications in the basal ganglia. There is a prolongation of the QT interval on the electrocardiogram, which disappears when the hypocalcemia is corrected. The electroencephalogram usually reveals widespread slow activity; the tracing returns to normal after the serum calcium concentration has been within the normal range for a few weeks, unless irreversible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. When hypoparathyroidism occurs concurrently with Addison disease, the serum level of calcium may be normal, but hypocalcemia appears after effective treatment of the adrenal insufficiency.

**Treatment**

Emergency treatment of neonatal tetany consists of intravenous injections of 5-10 mL or 1-3 mg/kg of a 10% solution of calcium gluconate (elemental calcium 9.3 mg/mL) at the rate of 0.5-1.0 mL/min while the heart rate is monitored and a total dose not to exceed 20 mg of elemental calcium/kg. Additionally, 1,25-dihydroxycholecalciferol (calcitriol) should be given. The initial dosage is 0.25 µg/24 hr; the maintenance dosage ranges from 0.01-0.10 µg/kg/24 hr to a maximum of 1-2 µg/24 hr. Calcitriol has a short half-life and should be given in 2 equal divided doses; it has the advantages of rapid onset of effect (1-4 days) and rapid reversal of hypercalcemia after discontinuation in the
event of overdosage (calcium levels begin to fall in 3-4 days). Calcitriol is supplied as an oral solution.

An adequate intake of calcium should be ensured. Supplemental calcium can be given in the form of calcium gluconate or calcium glubionate to provide 800 mg of elemental calcium daily, but it is rarely essential. Foods with high phosphorus content such as milk, eggs, and cheese should be reduced in the diet.

Clinical evaluation of the patient and frequent determinations of the serum calcium levels are indicated in the early stages of treatment to determine the requirement for calcitriol or vitamin D₃. If hypercalcemia occurs, therapy should be discontinued and resumed at a lower dose after the serum calcium level has returned to normal. In long-standing cases of hypercalcemia, repair of cerebral and dental changes is not likely. Pigmentation, lowering of blood pressure, or weight loss can indicate adrenal insufficiency, which requires specific treatment. Patients with autosomal dominant hypocalcemic hypercalciuria can develop nephrocalcinosis and renal impairment if treated with vitamin D.

**Differential Diagnosis**

Magnesium deficiency must be considered in patients with unexplained hypocalcemia. Concentrations of serum magnesium <1.5 mg/dL (1.2 mEq/L) are usually abnormal. Familial hypomagnesemia with secondary hypocalcemia has been reported in approximately 50 patients, most of whom developed tetany and seizures at 2-6 wk of age. Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. Oral supplements of magnesium are necessary to maintain levels of magnesium in the normal range. Two genetic forms have been described. One is caused by an autosomal recessive gene on chromosome 9, resulting in a specific defect in absorption of magnesium. The other is caused by an autosomal dominant gene on chromosome 11q23, resulting in renal loss of magnesium.

Hypomagnesemia also occurs in malabsorption syndromes such as Crohn disease and cystic fibrosis. Patients with autoimmune polyglandular disease type I and hypoparathyroidism can also have concurrent steatorrhea and low magnesium levels. Therapy with aminoglycosides causes hypomagnesemia by increasing urinary losses.

It is not clear how low levels of magnesium lead to hypocalcemia. Evidence suggests that hypomagnesemia impairs release of PTH and induces resistance to the effects of the hormone, but other mechanisms also may be operative.

Poisoning with inorganic phosphate leads to hypocalcemia and tetany. Infants administered large doses of inorganic phosphates, either as laxatives or as sodium phosphate enemas, have had sudden onset of tetany, with serum calcium levels <5 mg/dL and markedly elevated levels of phosphate. Symptoms are quickly relieved by intravenous administration of calcium. The mechanism of the hypocalcemia is not clear (see Chapter 55.6).

Hypocalcemia can occur early in the course of treatment of acute lymphoblastic leukemia. Hypocalcemia is usually associated with hyperphosphatemia resulting from destruction of lymphoblasts. Episodic symptomatic hypocalcemia occurs in the **Kenny-Caffey syndrome**, which is characterized by medullary stenosis of the long bones, short stature, delayed closure of the fontanel, delayed bone age, and eye abnormalities. Idiopathic hypoparathyroidism and abnormal PTH levels have been found. Autosomal dominant and autosomal recessive modes of inheritance have been reported. Mutations of the **TBCE** gene (1q 43-44) perturb microtubule organization in diseased cells.

*Bibliography is available at Expert Consult.*
Bibliography


In contrast to the situation in hypoparathyroidism, in pseudohypoparathyroidism (PHP) the parathyroid glands are normal or hyperplastic and they can synthesize and secrete parathyroid hormone (PTH). Serum levels of immunoreactive PTH are elevated even when the patient is hypocalcemic and may be elevated when the patient is normocalcemic. Neither endogenous nor administered PTH raises the serum levels of calcium or lowers the levels of phosphorus. The genetic defects in the hormone receptor adenylate cyclase system are classified into various types depending on the phenotypic and biochemical findings.

**TYPE IA**

Type Ia accounts for the majority of patients with PHP. Affected patients have a genetic defect of the \( \alpha \) subunit of the stimulatory guanine nucleotide-binding protein (\( G_\alpha \)). This coupling factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP). Heterogeneous mutations of the \( G_\alpha \) gene have been documented; the gene is located on chromosome 20q13.2. Deficiency of the \( G_\alpha \) subunit is a generalized cellular defect and accounts for the association of other endocrine disorders with type Ia PHP. The defect is inherited as an autosomal dominant trait, and the paucity of father-to-son transmissions is thought to be a result of decreased fertility in males.

Tetany is often the presenting sign. Affected children have a short, stocky build and a round face. Brachydactyly with dimpling of the dorsum of the hand is usually present. The 2nd metacarpal is involved least often. As a result, the index finger occasionally is longer than the middle finger. Likewise, the 2nd metatarsal is only rarely affected. There may be other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of the calvaria. These patients often have calcium deposits and metaplastic bone formation subcutaneously. Moderate degrees of cognitive impairment, calcification of the basal ganglia, and lenticular cataracts are common in patients whose disease is diagnosed late.

Some members of affected kindreds may have the usual anatomic stigmata of PHP, but serum levels of calcium and phosphorus are normal despite reduced \( G_\alpha \) activity; however, PTH levels may be slightly elevated. Such patients have been labeled as having pseudopseudohypoparathyroidism. Transition from normocalcemia to hypocalcemia often occurs with increasing age of the patient. These phenotypically similar but metabolically dissimilar patients may be in the same family and have the same mutations of \( G_\alpha \) protein. It is not known what other factors cause clinically overt hypocalcemia in some affected patients and not in others. There is some evidence to suggest that the \( G_\alpha \) mutation is paternally transmitted in pseudopseudohypoparathyroidism and maternally transmitted in patients with type Ia disease. The gene may be imprinted in a tissue-specific manner.

In addition to resistance to PTH, resistance to other G-protein-coupled receptors for thyroid-stimulating hormone (TSH), gonadotropins, and glucagon can result in various metabolic effects. Clinical hypothyroidism is uncommon, but basal levels of TSH are elevated
and thyrotropin-releasing hormone–stimulated TSH responses are exaggerated. Moderately decreased levels of thyroxine and increased levels of TSH have been demonstrated by newborn thyroid-screening programs, leading to the detection of type Ia PHP in infancy. In adults, gonadal dysfunction is common, as manifested by sexual immaturity, amenorrhea, oligomenorrhea, and infertility. Each of these abnormalities can be related to deficient synthesis of cAMP secondary to a deficiency of \(G_\alpha\), but it is not clear why resistance to other G-protein–dependent hormones (corticotropin, vasopressin) is much less affected.

Serum levels of calcium are low, and those of phosphorus and alkaline phosphatase are elevated. Clinical diagnosis can be confirmed by demonstration of a markedly attenuated response in urinary phosphate and cAMP after intravenous infusion of the synthetic 1-34 fragment of human PTH (teriparatide acetate). Definitive diagnosis is established by demonstration of the mutated G protein.

**Type Ia with Precocious Puberty**

Two boys have been reported with both type Ia PHP and gonadotropin-independent precocious puberty (see Chapter 562.7). They were found to have a temperature-sensitive mutation of the \(G_\alpha\) protein. Thus, at normal body temperature (37°C [98.6°F]), the \(G_\alpha\) is degraded, resulting in PHP, but in the cooler temperature of the testes (33°C [91.4°F]) the \(G_\alpha\) mutation results in constitutive activation of the luteinizing hormone receptor and precocious puberty.

**TYPE IB**

Affected patients have normal levels of G protein activity and a normal phenotypic appearance. These patients have tissue-specific resistance to PTH but not to other hormones. Serum levels of calcium, phosphorus, and immunoreactive PTH are the same as those in patients with type Ia PHP. These patients also show no rise in cAMP in response to exogenous administration of PTH. Bioactive PTH is not increased. The pathophysiology of the disorder in this group of patients is caused by paternal uniparental isodisomy of chromosome 20q and resulting \(GNAS1\) methylation. This, along with the loss of the maternal \(GNAS1\) gene, leads to PTH resistance in the proximal renal tubules, which leads to impaired mineral ion homeostasis.

**ACRODYSOSTOSIS WITH HORMONE RESISTANCE**

Patients with acrodysostosis resemble those with PHP type Ia, but defects in the \(G_\alpha\) subunit are not present. Instead, in 1 subgroup of patients there is a defect in the gene encoding \(PRKAR1A\), the cAMP-dependent regulatory subunit of protein kinase A that confers resistance to multiple hormones, including PTH. Another subgroup has a defect in a phosphodiesterase gene \(PDE4D\). This subgroup also carries the phenotype of PHP type Ia but rarely exhibits the hormone resistance.

*Bibliography is available at Expert Consult.*
Bibliography


Excessive production of parathyroid hormone (PTH) can result from a primary defect of the parathyroid glands such as an adenoma or hyperplasia (primary hyperparathyroidism). More often, the increased production of PTH is compensatory, usually aimed at correcting hypocalcemic states of diverse origins (secondary hyperparathyroidism). In vitamin D–deficient rickets and the malabsorption syndromes, intestinal absorption of calcium is deficient but hypocalcemia and tetany may be averted by increased activity of the parathyroid glands. In pseudohypoparathyroidism, PTH levels are elevated because a mutation in the G,α protein interferes with response to PTH. Early in chronic renal disease, hyperphosphatemia results in a reciprocal fall in the calcium concentration with a consequent increase in PTH, but in advanced stages of renal failure, production of 1,25(OH)₂D₃ is also decreased, leading to worsening hypocalcemia and further stimulation of PTH. In some instances, if stimulation of the parathyroid glands has been sufficiently intense and protracted, the glands continue to secrete increased levels of PTH for months or years after kidney transplantation, with resulting hypercalcemia.

ETIOLOGY
Childhood hyperparathyroidism is uncommon. Onset during childhood is usually the result of a single benign adenoma. It usually becomes manifested after 10 yr of age. There have been a number of kindreds in which multiple members have hyperparathyroidism transmitted in an autosomal dominant fashion. Most of the affected family members are adults, but children have been involved in approximately 30% of the pedigrees. Some affected patients in these families are asymptomatic, and disease is detected only by careful study. In other kindreds, hyperparathyroidism occurs as part of the constellation known as the multiple endocrine neoplasia (MEN) syndromes or of the hyperparathyroidism–jaw tumor syndrome.

Neonatal severe hyperparathyroidism is a rare disorder. Symptoms develop shortly after birth and consist of anorexia, irritability, lethargy, constipation, and failure to thrive. Radiographs reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures. Symptoms may be mild, resolving without treatment, or can have a rapidly fatal course if diagnosis and treatment are delayed. Histologically, the parathyroid glands show diffuse hyperplasia. Affected siblings have been observed in some kindreds, and parental consanguinity has been reported in several kindreds. Most cases have occurred in kindreds with the clinical and biochemical features of familial hypocalciuric hypercalcemia. Infants with neonatal severe hyperparathyroidism may be homozygous or heterozygous for the mutation in the Ca²⁺-sensing receptor gene, whereas most persons with 1 copy of this mutation exhibit autosomal dominant familial hypocalciuric hypercalcemia.

MEN type I is an autosomal dominant disorder characterized by hyperplasia or neoplasia of the endocrine pancreas (which secretes gastrin, insulin, pancreatic polypeptide, and occasionally glucagon), the anterior pituitary (which usually secretes prolactin), and the parathyroid glands. In most kindreds, hyperparathyroidism is usually the presenting manifestation, with a prevalence approaching 100% by 50 yr of age and occurring only rarely in children younger than 18 yr of age. With appropriate DNA probes, it is possible to detect carriers of the gene with 99% accuracy at birth, avoiding unnecessary biochemical screening programs.

The gene for MEN type I is on chromosome 11q13; it appears to function as a tumor-suppressor gene and follows the 2-hit hypothesis of tumor development. The first mutation (germinal) is inherited and is recessive to the dominant allele; this does not result in tumor formation. A second mutation (somatic) is required to eliminate the normal allele, which then leads to tumor formation.

Hyperparathyroidism–jaw tumor syndrome is an autosomal dominant disorder characterized by parathyroid adenomas and fibrousosseous jaw tumors. Affected patients can also have polycystic kidney disease, renal hamartomas, and Wilms tumor. Although the condition affects adults primarily, it has been diagnosed as early as age 10 yr.

MEN type II may also be associated with hyperparathyroidism (see Chapter 569.2).

Transient neonatal hyperparathyroidism has occurred in a few infants born to mothers with hypoparathyroidism (idiopathic or surgical) or with pseudohypoparathyroidism. In each case, the maternal disorder had been undiagnosed or inadequately treated during pregnancy. The cause of the condition is chronic intrauterine exposure to
hypocalcemia with resultant hyperplasia of the fetal parathyroid glands. In the newborn, manifestations involve the bones primarily, and healing occurs between 4 and 7 mo of age.

**CLINICAL MANIFESTATIONS**

At all ages, the clinical manifestations of hypercalcemia of any cause include muscle weakness, fatigue, headache, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia, polyuria, weight loss, and fever. When hypercalcemia is of long duration, calcium may be deposited in the renal parenchyma (nephrocalcinosis), with progressively diminished renal function. Renal calculi can develop and can cause renal colic and hematuria. Osseous changes can produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors. Height can decrease from compression of vertebrae; the patient can become bedridden. Detection of completely asymptomatic patients is increasing with the advent of automated panel assays that include serum calcium determinations.

Abdominal pain is occasionally prominent and may be associated with acute pancreatitis. Parathyroid crisis can occur, manifested by serum calcium levels >15 mg/dL and progressive oliguria, azotemia, stupor, and coma. In infants, failure to thrive, poor feeding, and hypotonia are common.

Cognitive impairment, convulsions, and blindness can occur as sequelae of long-standing hypercalcemia. Psychiatric manifestations include depression, confusion, dementia, stupor, and psychosis.

**LABORATORY FINDINGS**

The serum calcium level is elevated; 39 of 45 children with adenomas had levels >12 mg/dL. The hypercalcemia is more severe in infants with parathyroid hyperplasia; concentrations ranging from 15-20 mg/dL are common, and values as high as 30 mg/dL have been reported. Even when the total serum calcium level is borderline or only slightly elevated, ionized calcium levels are often increased. The serum phosphorus level is reduced to approximately 3 mg/dL or less, and the level of serum magnesium is low. The urine can have a low and fixed specific gravity, and serum levels of nonprotein nitrogen and uric acid may be elevated. In patients with adenomas who have skeletal involvement, serum phosphatase levels are elevated, but in infants with hyperplasia the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

Serum levels of intact PTH are elevated, especially in relation to the level of calcium. Calcitonin levels are normal. Acute hypercalcemia can stimulate calcitonin release, but with prolonged hypercalcemia, hypercalcitoninemia does not occur.

The most consistent and characteristic radiographic finding is resorption of subperiosteal bone, best seen along the margins of the phalanges of the hands. In the skull, there may be gross trabeculation or a granular appearance resulting from focal rarefaction; the lamina dura may be absent. In more advanced disease, there may be generalized rarefaction, cysts, tumors, fractures, and deformities. Approximately 10% of patients have radiographic signs of rickets. Radiographs of the abdomen can reveal renal calculi or nephrocalcinosis.

**DIFFERENTIAL DIAGNOSIS**

Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism (Table 573-1 and Fig. 573-1). A low serum phosphorus level with hypercalcemia is characteristic of primary hyperparathyroidism; elevated levels of PTH are also diagnostic. With hypercalcemia of any cause except hyperparathyroidism and familial hypocalciuric hypercalcemia, PTH levels are suppressed. Pharmacologic doses of corticosteroids lower the serum calcium level to normal in patients with hypercalcemia from other causes but generally do not affect the calcium level in patients with hyperparathyroidism.

**TREATMENT**

Surgical exploration is indicated in all instances. All glands should be carefully inspected; if an adenoma is discovered, it should be removed; very few instances of carcinoma are known in children. Most neonates with severe hypercalcemia require total parathyroidectomy; less-severe hypercalcemia remits spontaneously in others. Still others have been treated successfully with bisphosphonates and calcimimetics. The patient should be carefully observed postoperatively for the development of hypocalcemia and tetany; intravenous administration of calcium gluconate may be required for a few days. The serum calcium level then gradually returns to normal, and, under ordinary conditions, the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

![Figure 573-1 Evaluation of hypercalcemia. Ca²⁺, calcium ions; CaSR, calcium-sensing receptor; CMV, cytomegalovirus; FeCa, fractional excretion of urinary calcium.](From Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. Curr Opin Pediatr 22:508–515, 2010.)
# Causes of Hypercalcemia

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circumstances, a diet high in calcium and phosphorus must be maintained for only several months after operation.

CT, real-time ultrasonography, and subtraction scintigraphy using sestamibi/technetium-percstinate alone and in combination have proved effective in localizing a single adenoma vs diffuse hyperplasia in 50-90% of adults. Parathyroid surgeons often rely on intraoperative selective venous sampling with intraoperative assay of PTH for localizing and removing the source of increased PTH secretion.

**PROGNOSIS**

The prognosis is good if the disease is recognized early and there is appropriate surgical treatment. When extensive osseous lesions are present, deformities may be permanent. A search for other affected family members is indicated.

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**573.1 Other Causes of Hypercalcemia**

**Daniel A. Doyle**

### FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FAMILIAL BENIGN HYPERCALCEMIA)

Patients with familial hypocalciuric hypercalcemia are usually asymptomatic, and the hypercalcemia is identified by chance during routine investigation for other conditions. The parathyroid glands are normal, PTH levels are inappropriately normal, and subtotal parathyroidectomy does not correct the hypercalcemia. Serum levels of magnesium are high normal or mildly elevated. The ratio of calcium-to-creatinine clearance is usually decreased despite hypercalcemia.

The disorder is inherited in an autosomal dominant manner and is caused by a mutant gene on chromosome 3q2. Penetration is near 100%, and the disorder can be diagnosed early in childhood by serum and urinary calcium concentrations. Detection of other affected family members is important to avoid inappropriate parathyroid surgery. The defect is an inactivating mutation in the Ca-sensing receptor gene. This G-protein–coupled receptor senses the level of free Ca in the blood and triggers the pathway to increase extracellular Ca in the face of hypocalcemia. This receptor functions in the parathyroid and kidney to regulate calcium homeostasis; inactivating mutations lead to an increased set point with respect to serum Ca, resulting in mild to moderate hypercalcemia in heterozygotes.

### GRANULOMATOUS DISEASES

Hypercalcemia occurs in 30-50% of children with sarcoidosis and less often in patients with other granulomatous diseases such as tuberculosis. Levels of PTH are suppressed, and levels of 1,25(OH)D are elevated. The source of *ectopic* 1,25(OH)D is the activated macrophage, through stimulation by interferon-α from T lymphocytes, which are present in abundance in granulomatous lesions. Unlike renal tubular cells, the 1α-hydroxylase in macrophages is unresponsive to homeostatic regulation. Oral administration of prednisone (2 mg/kg/24 hr) lowers serum levels of 1,25(OH)D to normal and corrects the hypercalcemia.

### HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia often occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloblastoma, leukemia, Burkitt lymphoma, dysgerminoma, and rhabdomyosarcoma. Serum levels of PTH are rarely elevated. In most patients, the hypercalcemia associated with malignancy is caused by elevated levels of parathyroid hormone–related peptide and not PTH. Rarely, tumors produce 1,25(OH)D or PTH ectopically.

### MISCELLANEOUS CAUSES OF HYPERCALCEMIA

Hypercalcemia can occur in infants with subcutaneous fat necrosis. Levels of PTH are normal. In 1 infant, the level of 1,25(OH)D was elevated and biopsy of the skin lesion revealed granulomatous infiltration, suggesting that the mechanism of the hypercalcemia was akin to that seen in patients with other granulomatous disease. In another infant, although the level of 1,25(OH)D was normal, PTH was suppressed, suggesting the hypercalcemia was not related to PTH. Treatment with prednisone is effective.

**Hypophosphatemia**, especially the severe infantile form, is usually associated with mild to moderate hypercalcemia (see Chapter 705). Serum levels of phosphorus are normal, and those of alkaline phosphatase are subnormal. The bones exhibit rachitic-like lesions on radiographs. Urinary levels of phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5’-phosphate are elevated; each is a natural substrate to a tissue-nonspecific (liver, bone, kidney) alkaline phosphatase enzyme. Missense mutations of the tissue-nonspecific alkaline phosphatase enzyme gene result in an inactive enzyme in this autosomal recessive disorder.

**Idiopathic hypercalcemia of infancy** is manifested by failure to thrive and hypercalcemia during the 1st yr of life, followed by spontaneous remission. Serum levels of phosphorus and PTH are normal. The condition has been defined as resulting from increased absorption of calcium from decreased degradation of 1,25(OH)D. Mutations in the CYP24A1 gene that encode 25-hydroxyvitamin D 24-hydroxylase, the key enzyme in 1,25(OH)D degradation, cause excessive levels of the active vitamin D metabolite, which, in turn, causes hypercalcemia in a subset of infants who receive supplemental vitamin D. An excessive rise in the level of 1,25(OH)D in response to PTH administration has been reported years after the hypercalcemic phase.

Approximately 10% of patients with Williams syndrome also inconsistently exhibit associated infantile hypercalcemia. The phenotype consists of feeding difficulties, slow growth, elfin facies (small mandible, prominent maxilla, upturned nose), renovascular disorders, and a gregarious “cocktail party” personality. Cardiac lesions include supravalvular aortic stenosis, peripheral pulmonic stenosis, aortic hypoplasia, coronary artery stenosis, and atrial or ventricular septal defects. Nephrocalcinosis can develop if hypercalcemia persists. The IQ score of 50-70 is curiously accompanied by enhanced quantity and quality of vocabulary, auditory memory, and social use of language. A contiguous gene deletion syndrome with a submicroscopic deletion at chromosome 7q11.23, which includes deletion of 1 elastin allele, occurs in 90% of patients and seems to account for the vascular problems. Definitive diagnosis can be established by specific fluorescence in situ hybridization. The hypercalcemia and central nervous system symptoms may be caused by deletion of adjacent genes. Hypercalcemia has been successfully controlled with either prednisone or calcitonin.

**Hypervitaminosis D** resulting in hypercalcemia from drinking milk that has been incorrectly fortified with excessive amounts of vitamin D has been reported. Not all patients with hypervitaminosis D develop hypercalcemia. Affected infants can manifest failure to thrive, nephrocalcinosis, poor renal function, and osteosclerosis. Serum levels of 25(OH)D are a better indicator of hypervitaminosis D than levels of 1,25(OH)D, because 25(OH)D has a longer half-life.

**Prolonged immobilization** can lead to hypercalcemia and occasionally to decreased renal function, hypertension, and encelophalopathy. Children who have hypophosphatemic rickets and undergo surgery with subsequent long-term immobilization are at risk for hypercalcemia and should therefore have their vitamin D supplementation decreased or discontinued.

**Jansen-type metaphyseal chondrodysplasia** is a rare genetic disorder characterized by short-limbed dwarfism and severe but asymptomatic hypercalcemia (see Chapter 704). Circulating levels of PTH and parathyroid hormone–related peptide are undetectable. These patients have an activating PTH–parathyroid hormone–related peptide receptor mutation that results in aberrant calcium homeostasis and abnormalities of the growth plate.

**Bibliography** is available at Expert Consult.
Chapter 573 • Hyperparathyroidism

Bibliography


Disorders of the Adrenal Gland

Chapter 574
Physiology of the Adrenal Gland

574.1 Histology and Embryology
Perrin C. White

The adrenal gland is composed of 2 endocrine tissues: the medulla and the cortex. The chromaffin cells of the adrenal medulla are derived from neuroectoderm, whereas the cells of the adrenal cortex are derived from mesoderm. Mesodermal cells also contribute to the development of the gonads. The adrenal glands and gonads have certain common enzymes involved in steroid synthesis; an inborn error in steroidogenesis in one tissue can also be present in the other.

The adrenal cortex of the older child or adult consists of 3 zones: the zona glomerulosa, the outermost zone located immediately beneath the capsule; the zona fasciculata, the middle zone; and the zona reticularis, the innermost zone, lying next to the adrenal medulla. The zona fasciculata is the largest zone, constituting approximately 75% of the cortex; the zona glomerulosa constitutes approximately 15% and the zona reticularis approximately 10%. Glomerulosa cells are small, with a lower cytoplasmic:nuclear ratio, an intermediate number of lipid inclusions, and smaller nuclei containing more condensed chromatins than the cells of the other 2 zones. The cells of the zona fasciculata are large, with a high cytoplasmic:nuclear ratio and many lipid inclusions. The cells are arranged in radial cords. The cells of the zona reticularis are arranged in irregular anastomosing cords. The cytoplasmic: nuclear ratio is intermediate, and the compact cytoplasm has relatively little lipid content.

The zona glomerulosa synthesizes aldosterone, the most potent mineralocorticoid in humans. The zona fasciculata and zona reticularis synthesize the adrenal androgens.

The adrenal medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. Neuroendocrine cells are polyhedral, with abundant cytoplasm and small, pale-staining nuclei. Under the electron microscope, the cytoplasm contains many large secretory granules that contain catecholamines. Glial cells have less cytoplasm and more basophilic nuclei.

The primordium of the fetal adrenal gland can be recognized at 3-4 wk of gestation just cephalad to the developing mesonephros. At 5-6 wk, the gonadal ridge develops into the steroidogenic cells of the gonads and adrenal cortex; the adrenal and gonadal cells separate, the adrenal cells migrate retroperitoneally, and the gonadal cells migrate caudally. At 6-8 wk of gestation, the gland rapidly enlarges, the cells of the inner cortex differentiate to form the fetal zone, and the outer subcapsular rim remains as the definitive zone. The primordium of the adrenal cortex is invaded at this time by sympathetic neural elements that differentiate into the chromaffin cells capable of synthesizing and storing catecholamines. Catechol O-methyltransferase, which converts norepinephrine to epinephrine, is expressed later in gestation. By the end of the 8th wk of gestation, the encapsulated adrenal gland is associated with the upper pole of the kidney. By 8-10 wk of gestation, the cells of the fetal zone are capable of active steroidogenesis.

In the full-term infant, the combined weight of both adrenal glands is 7-9 g. At birth, the inner fetal cortex makes up approximately 80% of the gland and the outer “true” cortex, 20%. Within a few days the fetal cortex begins to involute, undergoing a 50% reduction by 1 mo of age. Conversely, the adrenal medulla is relatively small at birth and undergoes a proportionate increase in size over the 1st 6 mo after birth. By 1 yr, the adrenal glands each weigh <1 g. Adrenal growth thereafter results in adult adrenal glands reaching a combined weight of 8 g. The zonae fasciculata and glomerulosa are fully differentiated by about 3 yr of age. The zona reticularis is not fully developed until puberty.

Adrenocorticotropic hormone (ACTH) is essential for fetal adrenal growth and maturation; feedback regulation of ACTH by cortisol is apparently established by 8-10 wk of gestation. Additional factors important in fetal growth and steroidogenesis include placental chorionic gonadotropins and a number of peptide growth factors produced by the placenta and fetus.

Several transcription factors are critical for the development of the adrenal glands. The 3 transcription factors associated with adrenal hypoplasia in humans are steroidogenic factor-1 (SF-1; NR5A1), DAX-1 (dosage-sensitive sex reversal, adrenal hypoplasia congenita, X chromosome; NR0B1), and the GLI3 oncogene. Disruption of SF-1, encoded on chromosome 9q33, results in gonadal and often adrenal agenesis, absence of pituitary gonadotropes, and an underdeveloped ventral medial hypothalamus. In-frame deletions and frameshift and nonsense mutations of this gene are associated with 46,XX ovarian insufficiency and 46,XY gonadal dysgenesis. Mutations in the DAX1 gene, encoded on Xp21, result in adrenal hypoplasia congenita and hypogonadotrophic hypogonadism (see Chapter 575.1). Mutations in GLI3 on chromosome 7p13 cause Pallister-Hall syndrome, other features of which include hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly.

The postnatal adrenal cortex is not static but, in fact, is continually regenerated from a population of stem or progenitor cells under the adrenal capsule. These cells move radially inward (i.e., centripetally) and can differentiate into zona glomerulosa or fasciculata cells as needed in response to the appropriate trophic stimuli (see Chapter 574.3). Several signaling pathways, including sonic hedgehog and Wnt, regulate this process. Sonic hedgehog expression is restricted to the peripheral cortical cells that do not express high levels of steroidogenic genes but give rise to the underlying differentiated cells of the cortex. Wnt/β-catenin signaling maintains the undifferentiated state and adrenal fate of adrenocortical stem/progenitor cells, in part through induction of its target genes DAX1 and inhibin-α, respectively. Adrenal tumors can result from constitutive activation of the Wnt signaling pathway (see Chapter 579), whereas mutations of DAX1 lead to loss of the ability of the adrenal cortex to regenerate; this condition is termed adrenal hypoplasia congenita (see Chapter 575).

Bibliography is available at Expert Consult.

574.2 Adrenal Steroid Biosynthesis
Perrin C. White

Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 574-1). Although adrenal cortex cells can synthesize cholesterol de novo from acetate, circulating plasma lipoproteins provide most of the cholesterol for adrenal cortex hormone formation. Receptors for both low-density lipoprotein and high-density lipoprotein cholesterol are expressed on the surface of adrenocortical cells; the receptor is termed scavenger receptor class B, type I. Patients with familial hypercholesterolemia who lack low-density lipoprotein receptors have unimpaired adrenal steroidogenesis, suggesting that high-density lipoprotein is the more important source of cholesterol. Cholesterol is stored as cholesteryl esters in vesicles and subsequently hydrolyzed by cholesteryl ester hydrolases to liberate free cholesterol for steroid hormone synthesis.
Bibliography
The rate-limiting step of adrenal steroidogenesis is importation of cholesterol across the mitochondrial outer and inner membrane. This requires several proteins, particularly the steroidogenic acute regulatory (StAR) protein. The steroidogenic acute regulatory protein has a very short half-life, and its synthesis is rapidly induced by trophic factors (corticotropin); thus, it is the main short-term (minutes to hours) regulator of steroid hormone biosynthesis.

At the mitochondrial inner membrane, the side chain of cholesterol is cleaved to yield pregnenolone. This is catalyzed by the cholesterol side-chain cleavage enzyme (cholesterol desmolase, side-chain cleavage enzyme, P450sc, CYP11A1; the last term is the current systematic nomenclature), a cytochrome P450 (CYP) enzyme. Like other P450s, this is a membrane-bound hemoprotein with a molecular mass of approximately 50 kDa. It accepts electrons from a nicotinamide adenine dinucleotide–positive–dependent enzyme of the short-chain dehydrogenase/reductase type 2; SULT2A1, steroid sulfotransferase.

Deoxycorticosterone then reenters mitochondria and is converted to aldosterone by aldosterone synthase (P450aldo, CYP11B2), a P450 enzyme structurally related to cholesterol desmolase. Aldosterone synthase also carries out 3 successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde.

**ZONA FASCICULATA**

In the endoplasmic reticulum of the zona fasciculata, pregnenolone and progesterone are converted by 17α-hydroxylase (P450c17, CYP17) to 17-hydroxyprogrenolone and 17-hydroxyprogesterone, respectively. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-Hydroxyprogrenolone is converted to 17-hydroxyprogesterone and 11-deoxycortisol by the same 3β-hydroxysteroid and 21-hydroxylase enzymes, respectively, as are active in the zona glomerulosa. Thus, inherited disorders in these enzymes affect both aldosterone and cortisol synthesis (see Chapter 576). Finally, 11-deoxycortisol reenters mitochondria and is converted to cortisol by steroid 11β-hydroxylase (P450c11, CYP11B1). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity. Thus, under normal circumstances the zona fasciculata cannot synthesize aldosterone.

**ZONA GLOMERULOSA**

In the zona glomerulosa, pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase type 2, a nicotinamide adenine dinucleotide–positive–dependent enzyme of the short-chain dehydrogenase type. Progesterone is converted to 11-deoxycorticosterone by steroid 21-hydroxylase (P450c21, CYP21), which is another P450. Like other P450s in the endoplasmic reticulum, it uses an electron transport system with only 1 accessory protein, P450 oxidoreductase.

**ZONA RETICULARIS**

In the zona reticularis and to some extent in the zona fasciculata, the 17-hydroxylase (CYP17) enzyme has an additional activity, cleavage of the 17,20 carbon–carbon bond. This converts 17-hydroxyprogrenolone to dehydroepiandrosterone (DHEA). DHEA is converted to androsterone, 16α-hydroxylation, and 21-hydroxylation, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone. Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP 19, aromatase (P450arom); HSD3B1, 3β-hydroxysteroid dehydrogenase/Δ5,4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1 and HSD17B5 are 2 different 17-hydroxysteroid dehydrogenase enzymes; SRDS2A, steroid 5α-reductase type 2; SULT2A1, steroid sulfotransferase.
cause the release of CRH and AVP (see Chapter 556). AVP and CRH are secreted in the hypothalamic-portal circulation in a pulsatile manner. This pulsatile secretion appears to be responsible for the pulsatile (ultradian) release of ACTH. The circadian rhythm of corticotropin release is probably induced by a corresponding circadian rhythm of hypothalamic CRH secretion, regulated by the suprachiasmatic nucleus with input from other areas of the brain. Cortisol exerts a negative feedback effect on the synthesis and secretion of ACTH, CRH, and AVP. ACTH inhibits its own secretion, a feedback effect mediated at the level of the hypothalamus. Thus the secretion of cortisol is a result of the interaction of the hypothalamus, pituitary, and adrenal glands and other neural stimuli.

ACTH acts through a specific G-protein–coupled receptor (also termed melanocortin receptor-2, encoded by the MCR2 gene) to activate adenylate cyclase and increase levels of cyclic adenosine monophosphate. Cyclic adenosine monophosphate has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of steriodogenic acute regulatory protein. The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol. These transcriptional effects occur at least in part through increased activity of protein kinase A, which phosphorylates several transcriptional regulatory factors. MC2R trafficking and signaling are dependent on the MC2R accessory protein (MRAP). Mutations in either MC2R or MRAP can cause familial glucocorticoid deficiency (see Chapter 575).

**REGULATION OF ALDOSTERONE SECRETION**

The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by the renin–angiotensin system and by potassium levels, with ACTH having only a short-term effect. In response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. Renin is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an α2-globulin produced by the liver, to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide angiotensin II. Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensins II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensins II and III occupy a G-protein–coupled receptor activating phospholipase C. This protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol triphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated kinases. Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by calmodulin-activated kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis.

**FETOPLACENTAL UNIT**

Steroid synthesis in the fetal adrenal varies during gestation (see Figs. 574-1 and 574-2). Shortly after the fetal adrenal gland forms (wk 8–10), it efficiently secretes cortisol, which is able to negatively feedback on the fetal pituitary and hypothalamus to suppress ACTH secretion. This is critical time for differentiation of the external genitalia in both sexes (see Chapter 576.1); to prevent virilization, the female fetus must not be exposed to high levels of androgens of adrenal origin, and placental aromatase activity must remain low during this time to minimize conversion of testosterone to estradiol in male fetuses, which would interfere with masculinization. After wk 12, HSD3B activity in the fetal adrenal gland decreases and steroid sulfokinase activity increases. Thus, the major steroid products of the midgestation fetal adrenal gland are DHEA and DHEA sulfate (DHEAS) and, by 16α-hydroxylation in the liver, 16α-hydroxy DHEAS. Aromatase activity increases in the placenta at the same time, and steroid sulfatase activity is high as well. Thus, the placenta uses DHEA and DHEAS as substrates for estrone and estradiol and 16α-OH DHEAS as a substrate for estril. Cortisol activity is low during the 2nd trimester, which might serve to prevent premature secretion of surfactant by the developing fetal lungs; surfactant levels can affect the timing of parturition. As term approaches, fetal cortisol concentration increases as a result of increased cortisol secretion and decreased conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2). Low levels of aldosterone are produced in mid-gestation, but aldosterone secretory capacity increases near term.

Bibliography is available at Expert Consult.

**574.3 Regulation of the Adrenal Cortex**

Perrin C. White

**REGULATION OF CORTISOL SECRETION**

Glucocorticoid secretion is regulated mainly by ACTH (corticotropin), a 39-amino-acid peptide that is produced in the anterior pituitary. It is synthesized as part of a larger-molecular-weight precursor peptide known as proopiomelanocortin. This precursor peptide is also the source of β-lipotropin. ACTH and β-lipotropin are cleaved further to yield α- and β-melanocyte–stimulating hormone, corticotropin-like intermediate lobe peptide, γ-lipotropin, β- and γ-endorphin, and enkephalin (see Chapter 556).

ACTH is released in secretory bursts of varying amplitude throughout the day and night. The normal diurnal rhythm of cortisol secretion is caused by the varying amplitudes of ACTH pulses. Pulses of ACTH and cortisol occur every 30–120 min, are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 hr after sleep begins.

Corticotropin-releasing hormone (CRH), synthesized by neurons of the parvicellular division of the hypothalamic paraventricular nucleus, is the most important stimulator of ACTH secretion. Arginine vasopressin (AVP) augments CRH action. Neural stimuli from the brain

**Figure 574-2**

Relative levels of cortisol and dehydroepiandrosterone sulfate (DHEAS) secretion by the fetal adrenal cortex during gestation as well as postnatally. Approximate times of several events are shown. Vertical axis is logarithmic, but values are approximate. Horizontal axis is not to scale.
Bibliography


Bibliography
Steroid hormones act through several distinct receptors corresponding to the known biologic activities of the steroid hormones: glucocorticoid, mineralocorticoid, progestin, estrogen, and androgen. These receptors belong to a larger superfamily of nuclear transcriptional factors that include, among others, thyroid hormone and retinoic acid receptors. They have a common structure that includes a carboxyterminal ligand-binding domain and a midregion DNA-binding domain. The latter domain contains 2 zinc fingers, each of which consists of a loop of amino acids stabilized by 4 cysteine residues chelating a zinc ion.

Unliganded glucocorticoid and mineralocorticoid receptors are found mainly in the cytosol. Hormone molecules diffuse through the cell membrane and bind receptors, changing their conformation and causing them to be translocated to the nucleus, where they bind DNA at specific hormone-response elements. Bound receptors can recruit other transcriptional coregulatory factors to DNA.

Whereas different steroids can share bioactivities because of their ability to bind to the same receptor, a given steroid can exert diverse biologic effects in different tissues. The diversity of hormonal responses is determined by the different genes that are regulated by each hormone in different tissues. Additionally, different combinations of coregulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes can increase or decrease the affinity of steroids for their receptors and thus modulate their activity. 11β-Hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid. This increases local glucocorticoid concentrations in several tissues, especially the liver, where glucocorticoids maintain hepatic glucose output (see Chapter 575.4). Overexpression of this enzyme in adipose tissue can predispose to development of obesity. Conversely, HSD11B2 oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol (see Chapter 575.4).

Although corticosteroid receptors mainly act in the nucleus, some responses to both glucocorticoids and mineralocorticoids begin within minutes, an interval too short to be accounted for by increased gene transcription and protein synthesis. Such “nongenomic” effects can in some cases be mediated by cell membrane–associated isoforms of the classic glucocorticoid and mineralocorticoid receptors, which can couple to a variety of rapid intracellular signaling pathways such as G proteins. Direct interactions with other proteins, such as ion channels, have been documented as well, particularly in the nervous system.

** ACTIONS OF GLUCOCORTICOIDS**

Glucocorticoids are essential for survival. The term glucocorticoid refers to the glucose-regulating properties of these hormones. However, glucocorticoids have multiple effects on carbohydrate, lipid, and protein metabolism. They also regulate immune, circulatory, and renal function. They influence growth, development, bone metabolism, and central nervous system activity.

In stress situations, glucocorticoid secretion can increase up to 10-fold. This increase is believed to enhance survival through increased cardiac contractility, cardiac output, sensitivity to the pressor effects of catecholamines and other pressor hormones, work capacity of the skeletal muscles, and capacity to mobilize energy stores.

**Metabolic Effects**

The primary action of the glucocorticoids on carbohydrate metabolism is to increase glucose production by increasing hepatic gluconeogenesis. Glucocorticoids also increase cellular resistance to insulin, thereby decreasing entry of glucose into the cell. This inhibition of glucose uptake occurs in adipocytes, muscle cells, and fibroblasts. In addition to opposing insulin action, glucocorticoids can work in parallel with insulin to protect against long-term starvation by stimulating glycogen deposition and production in liver. Both hormones stimulate glycogen synthetase activity and decrease glycogen breakdown. Glucocorticoid excess can cause hyperglycemia, and glucocorticoid deficiency can cause hypoglycemia.

Glucocorticoids increase free fatty acid levels by enhancing lipolysis, decreasing cellular glucose uptake, and decreasing glycerol production, which is necessary for reesterification of fatty acids. This increase in lipolysis is also stimulated through the permissive enhancement of lipolytic action of other factors such as epinephrine. This action affects adipocytes differently according to their anatomic locations. In the patient with glucocorticoid excess, fat is lost in the extremities but it is increased in the trunk (centripetal obesity), neck, and face (moon facies). This may involve effects on adipocyte differentiation.

Glucocorticoids generally exert a catabolic or anabolic effect on protein metabolism. Proteolysis in fat, skeletal muscle, bone, lymphoid, and connective tissue increases amino acid substrates that can be used in gluconeogenesis. Cardiac muscle and the diaphragm are almost entirely spared from this catabolic effect.

**Circulatory and Renal Effects**

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index. Moreover, they have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood vessels. In the absence of glucocorticoids, decreased cardiac output and shock can develop; in states of glucocorticoid excess, hypertension is often observed. This may be a result of activation of the mineralocorticoid receptor (see Chapter 575.4), which occurs when renal HSD11B2 is saturated by excessive levels of glucocorticoids.

**Growth**

In excess, glucocorticoids inhibit linear growth and skeletal maturation in children, apparently through direct effects on the epiphyses. However, glucocorticoids are also necessary for normal growth and development. In the fetus and neonate, they accelerate the differentiation and development of various tissues, including the hepatic and gastrointestinal systems, as well as the production of surfactant in the fetal lung. Glucocorticoids are often given to pregnant women at risk for delivery of premature infants in an effort to accelerate these maturational processes (see Chapters 97.2 and 101.3).

**Immunologic Effects**

Glucocorticoids play a major role in immune regulation. They inhibit synthesis of glycolipids and prostaglandin precursors and the actions of bradykinin. They also block secretion and actions of histamine and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, and interleukin-6), thus diminishing inflammation. High doses of glucocorticoids deplete monocytes, eosinophils, and lymphocytes, especially T cells. They do so at least in part by inducing cell-cycle arrest in the G0 phase and by activating apoptosis through glucocorticoid receptor–mediated effects. The effects on lymphocytes are primarily exerted on T-helper 1 cells and hence on cellular immunity, whereas the T-helper 2 cells are spared, leading to a predominantly humoral immune response. Pharmacologic doses of glucocorticoids can also decrease the size of immunologic tissues (spleen, thymus, and lymph nodes).

Glucocorticoids increase circulating polymorphonuclear cell counts, mostly by preventing their egress from the circulation. Glucocorticoids decrease diapedesis, chemotaxis, and phagocytosis of polymorphonuclear cells. Thus, the mobility of these cells is altered such that they do not arrive at the site of inflammation to mount an appropriate immune response. High levels of glucocorticoids decrease inflammatory and cellular immune responses and increase susceptibility to certain bacterial, viral, fungal, and parasitic infections.

**Effects on Skin, Bone, and Calcium**

Glucocorticoids inhibit fibroblasts, leading to increased bruising and poor wound healing through cutaneous atrophy. This effect explains
the thinning of the skin and striae that are seen in patients with Cushing syndrome.

Glucocorticoids have the overall effect of decreasing serum calcium and have been used in emergency therapy for certain types of hypercalcemia. This hypocalcemic effect probably results from a decrease in the intestinal absorption of calcium and a decrease in the renal reabsorption of calcium and phosphorus. Serum calcium levels, however, generally do not fall below normal because of a secondary increase in parathyroid hormone secretion.

The most significant effect of long-term glucocorticoid excess on calcium and bone metabolism is osteoporosis. Glucocorticoids inhibit osteoblastic activity by decreasing the number and activity of osteoblasts. Glucocorticoids also decrease osteoclastic activity but to a lesser extent, leading to low bone turnover with an overall negative balance. The tendency of glucocorticoids to lower serum calcium and phosphate levels causes secondary hyperparathyroidism. These actions decrease bone accretion and cause a net loss of bone mineral. Compliance with oral bisphosphonates, agents that are effective against glucocorticoid-induced osteoporosis, is poor, but evidence suggests that yearly treatment with intravenous zoledrionic acid is just as effective.

Central Nervous System Effects
Glucocorticoids readily penetrate the blood–brain barrier and have direct effects on brain metabolism. They decrease certain types of central nervous system edema and are often used to treat increased intracranial pressure. They stimulate appetite and cause insomnia with a reduction in rapid eye movement sleep. There is an increase in irritability and emotional lability, with an impairment of memory and ability to concentrate. Mild to moderate glucocorticoid excess for a limited period often causes a feeling of euphoria or well-being, but glucocorticoid excess and deficiency can both be associated with clinical depression. Glucocorticoid excess produces psychosis in some patients.

Glucocorticoid effects in the brain are mediated largely through interactions with both the mineralocorticoid and glucocorticoid receptors (sometimes referred to in this context as type I and type II corticosteroid receptors, respectively). Activation of type II receptors increases sensitivity of hippocampal neurons to the neurotransmitter serotonin, which might help explain the euphoria associated with high doses of glucocorticoids. Glucocorticoids suppress release of CRH in the anterior hypothalamus, but they stimulate it in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, where it can mediate fear and anxiety states. Glucocorticoids and other steroids might have nongenomic effects by modulating activities of both N-methyl-D-aspartate receptors and 574.5 Adrenal Medulla

The principal hormones of the adrenal medulla are the physiologically active catecholamines: dopamine, norepinephrine, and epinephrine (Fig. 574-3). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in chromaffin tissue outside the adrenal medulla. Metabolites of catecholamines are excreted in the urine, principally 3-methoxy-4-hydroxymandelic acid, metanephrine,
Bibliography
and normetanephrine. Urinary metanephrines and catecholamines are measured to detect pheochromocytomas of the adrenal medulla and sympathetic nervous system (see Chapter 580).

The proportions of epinephrine and norepinephrine in the adrenal gland vary with age. In early fetal stages, there is practically no epinephrine; at birth, norepinephrine remains predominant. However in adults, norepinephrine accounts for only 10-30% of the pressor amines in the medulla.

The effects of catecholamines are mediated through a series of G-protein-coupled adrenergic receptors. Both epinephrine and norepinephrine raise the mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and calorigenic effects of norepinephrine are much less pronounced than are those of epinephrine.

Bibliography is available at Expert Consult.
Bibliography


In primary adrenal insufficiency, congenital or acquired lesions of the adrenal cortex prevent production of cortisol and often aldosterone (Table 575-1). Acquired primary adrenal insufficiency is termed Addison disease. Dysfunction of the anterior pituitary gland or hypothalamus can cause a deficiency of corticotropin (adrenocorticotropic hormone [ACTH]) and lead to hypofunction of the adrenal cortex, termed secondary adrenal insufficiency; the term tertiary adrenal insufficiency is sometimes used to denote cases arising from hypothalamic dysfunction (Table 575-2).
<table>
<thead>
<tr>
<th>Causes of Primary Adrenal Insufficiency</th>
<th>PATHOGENESIS OR GENETICS</th>
<th>CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONGENITAL ADRENAL HYPERPLASIA</strong></td>
<td></td>
<td>Hyperandrogenism, hyperandrogenism, hypertension</td>
</tr>
<tr>
<td>21-Hydroxylase deficiency</td>
<td>CYP21A2 mutations</td>
<td>Ambiguous genitalia in boys, postnatal virilization in girls</td>
</tr>
<tr>
<td>11β-Hydroxylase deficiency</td>
<td>CYP11B1 mutations</td>
<td>XY sex reversal, puberty delay in both sexes, hypertension</td>
</tr>
<tr>
<td>3β-Hydroxysteroid dehydrogenase type 2 deficiency</td>
<td>CYP17A1 mutations</td>
<td>Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia</td>
</tr>
<tr>
<td>17α-Hydroxylase deficiency</td>
<td>HSD3B2 mutations</td>
<td>XY sex reversal, XY sex reversal</td>
</tr>
<tr>
<td>P450 oxidoreductase deficiency</td>
<td>POR mutations</td>
<td></td>
</tr>
<tr>
<td>P450 side-chain cleavage deficiency</td>
<td>CYP11A1 mutations</td>
<td></td>
</tr>
<tr>
<td>Congenital lipid adrenal hyperplasia</td>
<td>STAR mutations</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER GENETIC DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenoleukodystrophy or adrenomyeloneuropathy</td>
<td>ABCD1 mutations</td>
<td>Weakness, spasticity, dementia, blindness, quadriaparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression</td>
</tr>
<tr>
<td>Triple A syndrome (Allgrove syndrome)</td>
<td>AAAS mutations</td>
<td>Achalasia, alacrima, cognitive deficits, neuromuscular deficits, hyperkeratosis</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>DHCR7 mutations</td>
<td>Craniofacial malformations, developmental delay growth failure, cholesterol deficiency</td>
</tr>
<tr>
<td>Wolman disease</td>
<td>LIPA mutations</td>
<td>Bilateral adrenal calcification, hepatosplenomegaly</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>Mitochondrial DNA deletions</td>
<td>External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders</td>
</tr>
<tr>
<td>Pallister-Hall syndrome</td>
<td>GLI3 mutations</td>
<td>Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly</td>
</tr>
<tr>
<td>IMAGe syndrome</td>
<td>CDKN1C mutations</td>
<td>Intrauterine growth retardation, metaphyseal dysplasia, genital abnormalities</td>
</tr>
<tr>
<td><strong>Adrenal Hypoplasia Congenita</strong></td>
<td>NR0B1 mutations</td>
<td>Hypogonadotropic hypogonadism in boys</td>
</tr>
<tr>
<td>X-linked</td>
<td>Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and NR0B1</td>
<td>Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation</td>
</tr>
<tr>
<td>Xp21 contiguous gene syndrome</td>
<td>NRSAT1 mutations</td>
<td>XY sex reversal</td>
</tr>
<tr>
<td>SF-1 linked</td>
<td>MC2R mutations</td>
<td>Tall stature, characteristic facial features, such as hypertelorism and frontal bossing</td>
</tr>
<tr>
<td><strong>Familial Glucocorticoid Deficiency or Corticotropin Insensitivity Syndromes</strong></td>
<td>MRAP mutations</td>
<td>Growth failure, increased chromosomal breakage, natural killer cell deficiency</td>
</tr>
<tr>
<td>Type 1</td>
<td>MCM4 mutations</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>NNT mutations</td>
<td></td>
</tr>
<tr>
<td>Variant of familial glucocorticoid deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant of familial glucocorticoid deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUTOIMMUNE</strong></td>
<td>Sporadic; associations with HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA4, PTPN22, CIITA, CLEC16A</td>
<td>None</td>
</tr>
<tr>
<td>Isolated</td>
<td>AIRE mutations</td>
<td>Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases</td>
</tr>
<tr>
<td>APS type 1 (APECED)</td>
<td></td>
<td>Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases</td>
</tr>
<tr>
<td>APS type 2</td>
<td></td>
<td>Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes</td>
</tr>
<tr>
<td>APS type 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INFECTIOUS</strong></td>
<td>Tuberculosis</td>
<td>Tuberculosis-associated manifestations in other organs Other AIDS-associated diseases</td>
</tr>
<tr>
<td>Tuberculous adrenalitis</td>
<td>HIV-1</td>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>AIDs</td>
<td>Histoplasmosis, cryptococcosis, coccidioidomycosis</td>
<td></td>
</tr>
<tr>
<td>Fungal adrenalitis</td>
<td><em>Neisseria meningitidis</em></td>
<td></td>
</tr>
<tr>
<td>Meningococcal sepsis (Waterhouse-Friderichsen syndrome), African trypanosomiatis</td>
<td><em>Trypanosoma brucei</em></td>
<td>Other trypanosomiasis-associated organ involvement</td>
</tr>
<tr>
<td><strong>OTHER ACQUIRED CAUSES</strong></td>
<td>Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome, traumatic birth, anticoagulation</td>
<td>Symptoms and signs of underlying disease</td>
</tr>
<tr>
<td>Bilateral adrenal hemorrhage</td>
<td></td>
<td>Symptoms and signs of underlying disease</td>
</tr>
<tr>
<td>Bilateral adrenal metastases</td>
<td>Mainly cancers of the lung, stomach, breast, and colon</td>
<td>Symptoms and signs of underlying disease</td>
</tr>
<tr>
<td>Bilateral adrenal infiltration</td>
<td>Primary adrenal lymphoma, amyloidosis, hemochromatosis, sarcoidosis (rare)</td>
<td>Symptoms and signs of underlying disease</td>
</tr>
<tr>
<td>Bilateral adrenalectomy</td>
<td></td>
<td>Symptoms and signs of underlying disease</td>
</tr>
</tbody>
</table>
The associated anterior and/or posterior hormone deficiencies may vary.

<table>
<thead>
<tr>
<th>Drug-Induced</th>
<th>Pathogenesis or Genetics</th>
<th>Clinical Features in Addition to Adrenal Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, fluconazole</td>
<td>Inhibition of 11β-hydroxylase (CYP11B1)</td>
<td>None, unless related to drug</td>
</tr>
<tr>
<td>Trilostane</td>
<td>Inhibition of 3β-hydroxysteroid dehydrogenase type 2</td>
<td>None, unless related to drug</td>
</tr>
<tr>
<td>Aminoglutethimide</td>
<td>Inhibition of cholesterol side chain cleavage enzyme (CYP11A1)</td>
<td>None, unless related to drug</td>
</tr>
<tr>
<td>Mitotane (o,p-DDD)</td>
<td>Cytotoxicity</td>
<td>None, unless related to drug</td>
</tr>
</tbody>
</table>

AAAS, achalasia, adrenocortical insufficiency, alacrima syndrome; ABCD, ATP-binding cassette, subfamily D; ABCG5, ATP-binding cassette, subfamily G, member 5; ABCG8, ATP-binding cassette, subfamily G, member 8; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; CITA, class II transactivator; CTLA-4, cytotoxic T-lymphocyte antigen 4; DHCGR, 7-dehydrocholesterol reductase; HLA, human leukocyte antigen; IMAGE, intrauterine growth restriction (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita (AHC), and genitourinary abnormalities; LIPA, lipase A; MC2R, melanocortin 2 receptor; MCM4, minichromosome maintenance complex component 4; MICA, major histocompatibility complex class I chain-related gene A; MRAP, melanocortin 2 receptor accessory protein; PTPN22, protein tyrosine phosphatase, non-receptor type 22; STARR, steroidogenic acute regulatory protein.

Primary adrenal insufficiency in children is most frequently caused by genetic conditions that are often but not always manifested in infancy and less often by acquired problems such as autoimmune conditions (Table 575-3). Susceptibility to autoimmune conditions often has a genetic basis, and so these distinctions are not absolute.

**INHERITED ETIOLOGIES**

**Inborn Defects of Steroidogenesis**
The most common causes of adrenocortical insufficiency in infancy are the salt-losing forms of congenital adrenal hyperplasia (see Chapter 576). Approximately 75% of infants with 21-hydroxylase deficiency, almost all infants with lipid adrenal hyperplasia, and most infants with a deficiency of 3β-hydroxysteroid dehydrogenase manifest salt-losing symptoms in the newborn period because they are unable to synthesize either cortisol or aldosterone.

**Adrenal Hypoplasia Congenita**
Adrenal hypoplasia congenita (AHC) is a relatively frequent cause of adrenal failure in boys along with congenital adrenal hyperplasia, autoimmune disease, and adrenoleukodystrophy. The name of the disorder notwithstanding, AHC is predominantly a failure of development of the definitive zone of the adrenal cortex; the fetal zone may be relatively normal. Consequently, adrenal insufficiency generally becomes evident as the fetal zone involutes postnatally (see Chapter 574), with onset in infancy or in the 1st 2 yr of life, but occasionally in later childhood or even adulthood. In some cases, aldosterone deficiency becomes evident before cortisol deficiency.

The disorder is caused by mutation of the \( \text{DAX1} (\text{NROB1}) \) gene, a member of the nuclear hormone receptor family, located on Xp21. Boys with AHC often do not undergo puberty owing to hypogonadotropic hypogonadism caused by the same mutated \( \text{DAX1} \) gene. Cryptorchidism, sometimes noted in these boys, is probably an early manifestation of hypogonadotropic hypogonadism, but often testicular function in infants is normal, with a typical or even an unusually prolonged testosterone surge in the 1st mo of life.

AHC occasionally occurs as part of a contiguous gene deletion syndrome together with Duchenne muscular dystrophy, glycerol kinase deficiency, cognitive impairment, or a combination of these conditions.

**Other Genetic Causes of Adrenal Hypoplasia**
The transcription factor SF-1 is required for adrenal and gonadal development (see Chapter 574). Males with a heterozygous mutation in SF-1 (NR5A1) have impaired development of the testes despite the presence of a normal copy of the gene on the other chromosome and can appear to be female, similar to patients with lipoid adrenal hyperplasia (see Chapter 576). Rarely, such patients have adrenal insufficiency as well.

Adrenal hypoplasia is also occasionally seen in patients with Pallister-Hall syndrome caused by mutations in the GLI3 oncogene (see Chapter 575).

**Adrenoleukodystrophy**
In adrenoleukodystrophy (ALD), adrenocortical deficiency is associated with demyelination in the central nervous system (see Chapters 86.2 and 599.3). High levels of very-long-chain fatty acids are found in tissues and body fluids, resulting from their impaired \( \beta \)-oxidation in the peroxisomes.

The most common form of ALD is an X-linked disorder with various presentations. The most common clinical picture is of a degenerative neurologic disorder appearing in childhood or adolescence and progressing to severe dementia and deterioration of vision, hearing, speech, and gait, with death occurring within a few years. Neurologic symptoms may be subtle at onset, sometimes consisting only of behavioral changes or deteriorating academic performance. Generalized but incomplete alopecia, resembling that of chemotherapy, is a characteristic but inconsistent finding. A milder form of X-linked ALD is adrenomyeloneuropathy, which begins in later childhood or early adulthood. Patients may have evidence of adrenal insufficiency before, at the time of, or after neurologic symptoms develop, often with years separating their presentation. X-linked ALD is caused by mutations in the \( ABCD1 \) gene located on Xq28. The gene encodes a transmembrane transporter involved in the importation of very-long-chain fatty acids into peroxisomes. More than 400 mutations have been described in patients with X-linked ALD. Clinical phenotypes can vary even within families, perhaps owing to modifier genes or other unknown factors. There is no correlation between the degree of neurologic impairment and severity of adrenal insufficiency. Prenatal diagnosis by DNA analysis and family screening by very-long-chain fatty acid assays and mutation analysis are available. Women who are heterozygous carriers of the X-linked ALD gene can develop symptoms in midlife or later; adrenal insufficiency is rare.

Neonatal ALD is a rare autosomal recessive disorder. Infants have neurologic deterioration and have or acquire evidence of adrenocortical dysfuncion. Most patients have severe, progressive cognitive impairment and die before 5 yr of age. This disorder is a subset of Zellweger (cerebrohepatorenal) syndrome, in which peroxisomes do not develop at all owing to mutations in any of several genes (\( \text{PEX5}, \text{PEX1}, \text{PEX10}, \text{PEX13}, \text{and} \text{PEX26} \)) controlling the development of this organelle.

**Familial Glucocorticoid Deficiency**
Familial glucocorticoid deficiency is a form of chronic adrenal insufficiency characterized by isolated deficiency of glucocorticoids, elevated levels of ACTH, and generally normal aldosterone production, although salt-losing manifestations as are present in most other forms of adrenal insufficiency occasionally occur. Patients mainly have hypoglycemia, seizures, and increased pigmentation during the 1st decade of life. The disorder affects both sexes equally and is inherited in an autosomal recessive manner. There is marked adrenocortical atrophy with relative sparing of the zona glomerulosa. Mutations in the gene for the ACTH receptor (\( \text{MCR2} \)) have been described in approximately 25% of these patients, most of which affect trafficking of receptor molecules from the endoplasmic reticulum to the cell surface. Another 20% of cases are caused by mutations in \( \text{MRAP} \), which encodes a melanocyte receptor accessory protein required for this trafficking. Recently, mutations at new genetic loci have been identified, including

### Table 575-3: Frequencies of Etiologies of Primary Adrenal Insufficiency

<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>AGE AT DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>59% Infancy</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>16% Childhood-adolescence</td>
</tr>
<tr>
<td>APECED (autoimmune polycrinopathy-candidiasis-ectodermal dystrophy)</td>
<td>6% Childhood-adolescence</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>4% Childhood-adolescence</td>
</tr>
<tr>
<td>Isolated glucocorticoid deficiency</td>
<td>4% Infancy</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4% Childhood</td>
</tr>
<tr>
<td>Syndromes</td>
<td>3% Infancy</td>
</tr>
<tr>
<td>X-linked adrenal hypoplasia congenita</td>
<td>2% Infancy-childhood</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1% Infancy</td>
</tr>
</tbody>
</table>

the minichromosome maintenance-deficient 4 homolog (MCM4) and nicotinamide nucleotide transhydrogenase (NNT). These genes are involved in DNA replication and antioxidant defense, respectively. Patients with MCM4 mutations also have growth failure, increased chromosomal breakage, and natural killer cell deficiency.

Another syndrome of ACTH resistance occurs in association with achalasia of the gastric cardia and alacrima (triple A or Allgrove syndrome). These patients often have a progressive neurologic disorder that includes autonomic dysfunction, intellectual disability, motor neuropathy, and occasional deafness. This syndrome is also inherited in an autosomal recessive fashion, and the AAS gene has been mapped to chromosome 12q13. The encoded protein, aladin, might help regulate nucleocytoplasmic transport of other proteins.

**Type I Autoimmune Polyendocrinopathy**

Although autoimmune Addison disease most often occurs sporadically (see “Autoimmune Addison Disease” in Chapter 575.1), it can occur as a component of 2 syndromes, each consisting of a constellation of autoimmune disorders (see Chapter 566). Type I autoimmune polyendocrinopathy (APS-1), also known as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome, is inherited in a mendelian autosomal recessive manner, whereas APS-2 (see “Autoimmune Addison Disease” in Chapter 575.1) has complex inheritance. Chronic mucocutaneous candidiasis is most often the first manifestation of APS-1, followed by hypoparathyroidism and then by Addison disease, which typically develops in early adolescence. Other closely associated autoimmune disorders include gonadal failure, alopecia, vitiligo, keratopathy, enamel hypoplasia, nail dystrophy, intestinal malabsorption, and chronic active hepatitis. Hypothyroidism and type 1 diabetes mellitus occur in less than 10% of affected patients. Some components of the syndrome continue to develop as late as the 5th decade. Patients with APS-1 may have autoantibodies to the adrenal cytochrome P450 enzymes CYP21, CYP17, and CYP11A1. The presence of such antibodies indicates a high likelihood of the development of Addison disease or, in female patients, ovarian failure. Adrenal failure can evolve rapidly in APS-1; death in patients with a previous diagnosis and unexplained deaths in siblings of patients with APS-1 have been reported, indicating the need to closely monitor patients with APS-1 and to thoroughly evaluate apparently unaffected siblings of patients with this disorder.

The gene affected in APS-1 is designated autoimmune regulator-1 (AIRE1); it has been mapped to chromosome 21q22.3. The AIRE1 gene encodes a transcription factor that controls the expression of many proteins within the thymus, thus playing a critical role in the generation of immune tolerance. Many different mutations in the AIRE1 gene have been described in patients with APS-1, with 2 mutations (R257X and a 3-bp deletion) being most common. There has been autosomal dominant transmission in 1 kindred owing to a specific missense mutation (G228W).

**Disorders of Cholesterol Synthesis and Metabolism**

Patients with disorders of cholesterol synthesis or metabolism, including abetalipoproteinemia with deficient lipoprotein B-containing lipoproteins, and familial hypercholesterolemia, with decreased or impaired low-density lipoprotein receptors, have limited adrenocortical function. Adrenal insufficiency has been reported in patients with Smith-Lemli-Opitz syndrome, an autosomal recessive disorder manifesting with facial anomalies, microcephaly, limb abnormalities, and developmental delay (see Chapter 86.3). Mutations in the gene coding for sterol Δ′-reductase, mapped to 11q12-q13, resulting in impairment of the final step in cholesterol synthesis with marked elevation of 7-dehydrocholesterol, abnormally low cholesterol, and adrenal insufficiency, have been identified in Smith-Lemli-Opitz syndrome. Wolman disease is a rare autosomal recessive disorder caused by mutations in the gene encoding human lysosomal acid lipase on chromosome 10q23.2-23.3. Cholesteryl esters accumulate in lysosomes in most organ systems, leading to organ failure. Infants during the 1st or 2nd mo of life have hepatosplenomegaly, steatorrhea, abdominal distention, and failure to thrive. Adrenal insufficiency and bilateral adrenal calcification are present, and death usually occurs in the 1st yr of life.

**Corticosteroid-Binding Globulin Deficiency and Decreased Cortisol-Binding Affinity**

Corticosteroid-binding globulin deficiency and decreased cortisol-binding affinity result in low levels of plasma cortisol but normal urinary free cortisol and normal plasma ACTH levels. A high prevalence of hypotension and fatigue has been reported in some adults with abnormalities of corticosteroid-binding globulin deficiency.

**ACQUIRED ETIOLOGIES**

**Autoimmune Addison Disease**

The most common cause of Addison disease is autoimmune destruction of the glands. The glands may be so small that they are not visible at autopsy, and only remnants of tissue are found in microscopic sections. Usually, the medulla is not destroyed, and there is marked lymphocytic infiltration in the area of the former cortex. In advanced disease, all adrenocortical function is lost, but early in the clinical course, isolated cortisol deficiency can occur. Most patients have anti-adrenal cytoplasmic antibodies in their plasma; 21-hydroxylase (CYP21) is the most commonly occurring biochemically defined autoantigen.

Addison disease can occur as a component of 2 autoimmune polyendocrinopathy syndromes. Type 1 (APS-1) was discussed previously. **Type II autoimmune polyendocrinopathy** (APS-2) consists of Addison disease associated with autoimmune thyroid disease (Schmidt syndrome) or type 1 diabetes (Carpenter syndrome). Gonadal failure, vitiligo, alopecia, and chronic atrophic gastritis, with or without pernicious anemia, can occur. Frequencies of the human leukocyte antigen (HLA)-D3 and HLA-D4 alleles are increased in these patients and appear to confer an increased risk for development of this disease; particular alleles at the major histocompatibility complex class I–related genes A and B (MICA and MICB) also are associated with this disorder. Polymorphisms in genes involved in other autoimmune disorders have been inconsistently associated with primary adrenal insufficiency, and their contribution to its pathogenesis must be regarded as uncertain. These include the class II, major histocompatibility complex, transactivator (CIITA), C-type lectin domain family 16, member A (CLEC16A), and protein tyrosine phosphatase, non-receptor type 22 (PTPN22). The disorder is most common in middle-aged women and can occur in many generations of the same family. Antiadrenal antibodies, specifically antibodies to the CYP21, CYP17, and CYP11A1 enzymes, are also found in these patients. Autoimmune adrenal insufficiency may also be seen in patients with celiac disease (see Chapter 338.2).

**Infection**

Tuberculosis was a common cause of adrenal destruction in the past but is much less prevalent now. The most common infectious etiology for adrenal insufficiency is meningococcemia (see Chapter 191); adrenal crisis from this cause is referred to as the Waterhouse-Friderichsen syndrome. Patients with AIDS can have a variety of subclinical abnormalities in the hypothalamic-pituitary-adrenal axis, but frank adrenal insufficiency is rare. However, drugs used in the treatment of AIDS can affect adrenal hormone homeostasis.

**Drugs**

Ketoconazole, an antifungal drug, can cause adrenal insufficiency by inhibiting adrenal enzymes. Mitotane (o,p′-DDD), used in the treatment of adrenocortical carcinoma and refractory Cushing syndrome (see Chapters 577 and 579), is cytotoxic to the adrenal cortex and can also alter extraadrenal cortisol metabolism. Signs of adrenal insufficiency occur in a substantial percentage of patients treated with mitotane. Etomidate, used in the induction and maintenance of general anesthesia, inhibits 11β-hydroxylase (CYP11B1), and a single induction dose can block cortisol synthesis for 4–8 hr or longer. This may be problematic in severely stressed patients, particularly if repeated doses
are used in a critical care setting. Although not themselves a cause of adrenal insufficiency, rifampicine and anticonvulsives such as phenytoin and phenobarbital reduce the effectiveness and bioavailability of corticosteroid replacement therapy by inducing steroid metabolizing enzymes in the liver.

**Hemorrhage into Adrenal Glands**

Hemorrhage into adrenal glands can occur in the neonatal period as a consequence of a difficult labor (especially breech presentation), or its etiology might not be apparent (Fig. 575–1). An incidence rate of 3 in 100,000 live births has been suggested. The hemorrhage may be sufficiently extensive to result in death from exsanguination or hypoadrenalism. An abdominal mass, anemia, unexplained jaundice, or scrotal hematoma may be the presenting sign. Often, the hemorrhage is asymptomatic initially and is identified later by calcification of the adrenal gland. Fetal adrenal hemorrhage has also been reported. Postnatally, adrenal hemorrhage most often occurs in patients being treated with anticoagulants. It can also occur as a result of child abuse.

**Clinical Manifestations**

Primary adrenal insufficiency leads to cortisol and often aldosterone deficiency. The signs and symptoms of adrenal insufficiency are most easily understood in the context of the normal actions of these hormones (see Chapter 574; Table 575–4).

Hypoglycemia is a prominent feature of adrenal insufficiency. It is often accompanied by ketosis as the body attempts to use fatty acids as an alternative energy source. Ketosis is aggravated by anorexia, nausea, and vomiting, all of which occur frequently.

Cortisol deficiency decreases cardiac output and vascular tone; moreover, catecholamines such as epinephrine have decreased inotropic and pressor effects in the absence of cortisol. These problems are initially manifested as orthostatic hypotension in older children and can progress to frank shock in patients of any age. They are exacerbated by aldosterone deficiency, which results in hypovolemia owing to decreased resorption of sodium in the distal nephron.

Hypotension and decreased cardiac output decrease glomerular filtration and thus decrease the ability of the kidney to excrete free water. Vasopressin (AVP) is secreted by the posterior pituitary in response to hypotension and also as a direct consequence of lack of inhibition by cortisol. These factors decrease plasma osmolality and lead in particular to hyponatremia. Hyponatremia is also caused by aldosterone deficiency and may be much worse when both cortisol and aldosterone are deficient.

In addition to hypovolemia and hyponatremia, aldosterone deficiency causes hyperkalemia by decreasing potassium excretion.

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**Table 575-4** Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>PATHOPHYSIOLOGIC MECHANISM</th>
<th>PREVALENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Glucocorticoid deficiency</td>
<td>90</td>
</tr>
<tr>
<td>Anorexia, weight loss</td>
<td>Glucocorticoid deficiency</td>
<td>90</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Glucocorticoid deficiency, mineralocorticoid deficiency</td>
<td>90</td>
</tr>
<tr>
<td>Salt craving (primary adrenal insufficiency only)</td>
<td>Mineralocorticoid deficiency</td>
<td>20</td>
</tr>
<tr>
<td>Myalgia or joint pain</td>
<td>Glucocorticoid deficiency</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood pressure, orthostatic hypotension</td>
<td>Mineralocorticoid deficiency, glucocorticoid deficiency</td>
<td>70-100%</td>
</tr>
<tr>
<td>Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)</td>
<td>Excess of proopiomelanocortin-derived peptides</td>
<td>70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LABORATORY FINDINGS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)</td>
<td>90</td>
</tr>
<tr>
<td>Hyperkalemia (primary adrenal insufficiency only)</td>
<td>Mineralocorticoid deficiency</td>
<td>50</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Glucocorticoid deficiency</td>
<td>30</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Glucocorticoid deficiency</td>
<td>30</td>
</tr>
<tr>
<td>Ketosis</td>
<td>Glucocorticoid deficiency</td>
<td>80</td>
</tr>
<tr>
<td>Low random cortisol level</td>
<td>Glucocorticoid deficiency</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia, lymphocytosis</td>
<td>Glucocorticoid deficiency</td>
<td></td>
</tr>
<tr>
<td>High ACTH level (primary adrenal insufficiency only)</td>
<td>Glucocorticoid deficiency</td>
<td>100</td>
</tr>
<tr>
<td>High plasma renin activity (primary adrenal insufficiency only)</td>
<td>Mineralocorticoid deficiency</td>
<td>100</td>
</tr>
</tbody>
</table>

*Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.

in the distal nephron. Cortisol deficiency alone does not cause hyperkalemia.

Cortisol deficiency decreases negative feedback on the hypothalamus and pituitary, leading to increased secretion of ACTH. Hyperpigmentation is caused by ACTH and other peptide hormones (γ-melanocyte-stimulating hormone) arising from the ACTH precursor proopiomelanocortin. In patients with a fair complexion, the skin can have a bronze cast. Pigmentation may be more prominent in skin creases, mucosa, and scars. In dark-skinned patients, it may be most readily appreciated in the gingival and buccal mucosa.

The clinical presentation of adrenal insufficiency depends on the age of the patient, whether both cortisol and aldosterone secretion are affected, and to some extent on the underlying etiology. The most common causes in early infancy are inborn errors of steroid biosynthesis, sepsis, AHC, and adrenal hemorrhage. Infants have a relatively greater requirement for aldosterone than do older children, possibly owing to immaturity of the kidney and also to the low sodium content of human breast milk and infant formula. Hyperkalemia, hyponatremia, and hypoglycemia are prominent presenting signs of adrenal insufficiency in infants. Ketosis is not consistently present because infants generate ketones less well than do older children. Hyperpigmentation is not usually seen because this takes weeks or months to develop, and orthostatic hypotension is obviously difficult to demonstrate in infants.

Infants can become ill very quickly. There may be only a few days of decreased activity, anorexia, and vomiting before critical electrolyte abnormalities develop. In older children with Addison disease, symptoms include muscle weakness, malaise, anorexia, vomiting, weight loss, and orthostatic hypotension. These may be of insidious onset. It is not unusual to elicit, in retrospect, an episodic history spanning years with symptoms being noticeable only during intercurrent illnesses. Such patients can present with acute decompensation (adrenal crisis) during relatively minor infectious illnesses. Some of these patients have been initially misdiagnosed with chronic fatigue syndrome, postmononucleosis syndrome, chronic Lyme disease, or psychiatric disorders (depression or anorexia nervosa).

Hyperpigmentation is often, but not necessarily, present. Hyponatremia is present at diagnosis in almost 90% of patients. Hyperkalemia tends to occur later in the course of the disease in older children than in infants and is present in only half of patients at diagnosis. Normal potassium levels must never be presumed to rule out primary adrenal insufficiency.

Hypoglycemia and ketosis are common. Thus, the clinical presentation can be easily confused with gastroenteritis or other acute infections. Chronicity of symptoms can alert the clinician to the possibility of Addison disease, but this diagnosis should be considered in any child with orthostatic hypotension, hyponatremia, hypoglycemia, and ketosis. Salt craving is seen in primary adrenal insufficiency with mineralocorticoid deficiency. Fatigue, myalgias, fever, eosinophilia, lymphocytosis, hypercalcemia, and anemia may be noted with glucocorticoid deficiency.

**LABORATORY FINDINGS**

Hypoglycemia, ketosis, hyponatremia, and hyperkalemia have been discussed. An electrocardiogram is useful for quickly detecting hyperkalemia in a critically ill child. Acidosis is often present, and the blood urea nitrogen level is elevated if the patient is dehydrated.

Cortisol levels are sometimes at the low end of the normal range but are invariably low when the patient's degree of illness is considered. ACTH levels are high in primary adrenal insufficiency but can take time to be reported by the laboratory. Similarly, aldosterone levels may be within the normal range but inappropriately low considering the patient's hyponatremia, hyperkalemia, and hypovolemia. Plasma renin activity is elevated. Blood eosinophils may be increased in number, but this is rarely useful diagnostically.

Urinary excretion of sodium and chloride are increased and urinary potassium is decreased, but these are difficult to assess on random urine samples. Accurate interpretation of urinary electrolytes requires more-prolonged (24 hr) urine collections and knowledge of the patient's sodium and potassium intake.

The *most definitive* test for adrenal insufficiency is measurement of serum levels of cortisol before and after administration of ACTH; resting levels are low and do not increase normally after administration of ACTH. Occasionally, normal resting levels that do not increase after administration of ACTH can indicate an absence of adrenocortical reserve. A low initial level followed by a significant response to ACTH can indicate secondary adrenal insufficiency. Traditionally, this test has been performed by measuring cortisol levels before and 30 or 60 min after giving 0.250 mg of cosyntropin (ACTH 1-24) by rapid intravenous infusion. Aldosterone will transiently increase in response to this dose of ACTH and may also be measured. A low-dose test (1 µg ACTH 1-24/1.73 m²) is a more sensitive test of pituitary-adrenal reserve, but it has somewhat lower specificity (more false-positive tests).

**DIFFERENTIAL DIAGNOSIS**

Upon presentation, Addison disease often needs to be distinguished from more acute illnesses such as gastroenteritis with dehydration or sepsis. Additional testing is directed at identifying the specific cause for adrenal insufficiency. When congenital adrenal hyperplasia is suspected, serum levels of cortisol precursors (17-hydroxprogesterone) should be measured along with cortisol in an ACTH stimulation test (see Chapter 576). Elevated levels of very-long-chain fatty acids are diagnostic of ALD (see Chapter 599.3). Many genetic etiologies for primary adrenal insufficiency may be identified by direct genetic testing, but it can take many weeks for results to become available. The presence of antidiuretic antibodies suggests an autoimmune pathogenesis. Patients with autoimmune Addison disease must be closely observed for the development of other autoimmune disorders. In children, hypoparathyroidism is the most commonly associated disorder, and it is suspected if hypocalcemia and elevated phosphate levels are present.

Ultrasonography (which requires an experienced operator), CT, or MRI can help define the size of the adrenal glands.

**TREATMENT**

Treatment of acute adrenal insufficiency must be immediate and vigorous. If the diagnosis of adrenal insufficiency has not been established, a blood sample should be obtained before therapy to determine electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma renin activity. If the patient's condition permits, an ACTH stimulation test can be performed while initial fluid resuscitation is under way. An intravenous solution of 5% glucose in 0.9% saline should be administered to correct hypoglycemia, hypovolemia, and hyponatremia. Hypotonic fluids (e.g., 5% glucose in water or 0.2% saline) must be avoided because they can precipitate or exacerbate hyperkalemia. If hyperkalemia is severe, it can require treatment with intravenous calcium and/or bicarbonate, intrarectal potassium-binding resin (Kayexalate), or intravenous infusion of glucose and insulin. A watersoluble form of hydrocortisone, such as hydrocortisone sodium succinate, should be given intravenously. As much as 10 mg for infants, 25 mg for toddlers, 50 mg for older children, and 100 mg for adolescents should be administered as a bolus and a similar total amount given in divided doses at 6 hr intervals for the 1st 24 hr. These doses may be reduced during the next 24 hr if progress is satisfactory. Adequate fluid and sodium repletion is achieved by intravenous saline administration, aided by the mineralocorticoid effect of high doses of hydrocortisone.

Particular caution should be exercised in the rare patient with concomitant adrenal insufficiency and hypothyroidism, because thyroxine can increase cortisol clearance. Thus, an adrenal crisis may be precipitated if hypothyroidism is treated without first ensuring adequate glucocorticoid replacement.

After the acute manifestations are under control, most patients require chronic replacement therapy for their cortisol and aldosterone deficiencies. Hydrocortisone (cortisol) may be given orally in daily doses of 10 mg/m²/24 hr in 3 divided doses; some patients require 15 mg/m²/24 hr to minimize fatigue, especially in the morning.
Timed-release preparations of hydrocortisone are undergoing clinical trials but are not yet generally available. Equivalent doses (20-25% of the hydrocortisone dose) of prednisone or prednisolone may be divided and given twice daily. ACTH levels may be used to monitor adequacy of glucocorticoid replacement in primary adrenal insufficiency; in congenital adrenal hyperplasia, levels of precursor hormones are used instead (see Chapter 576). Blood samples for monitoring should be obtained at a consistent time of day and in a consistent relation to (i.e., before or after) the hydrocortisone dose. Normalizing ACTH levels is unnecessary under these circumstances. Excessive doses of hydrocortisone; generally morning ACTH levels high in the normal range to 3-4 times normal are satisfactory. Because untreated or severely undertreated patients can acutely decompensate during relatively minor illnesses, assessment of symptoms (or lack thereof) must not be used as a substitute for biochemical monitoring. During situations of stress, such as periods of infection or minor operative procedures, the dose of hydrocortisone should be increased 2-3-fold. Major surgery under general anesthesia requires high intravenous doses of hydrocortisone similar to those used for acute adrenal insufficiency.

If aldosterone deficiency is present, fludrocortisone, a synthetic mineralocorticoid, is given orally in doses of 0.05-0.2 mg daily. Measurements of plasma renin activity are useful in monitoring the adequacy of mineralocorticoid replacement. Chronic overdosage with glucocorticoids leads to obesity, short stature, and osteoporosis, whereas overdosage with fludrocortisone results in hypertension and occasionally hypokalemia.

Replacement of dehydroepiandrosterone (DHEA) in adults remains controversial; prepubertal children do not normally secrete large amounts of DHEA. Many adults with Addison disease complain of having decreased energy, and replacing DHEA can improve this problem, particularly in women in whom adrenal androgens represent approximately 50% of total androgen secretion.

Additional therapy might need to be directed at the underlying cause of the adrenal insufficiency in regard to infections and certain metabolic defects. Therapeutic approaches to ALD include administration of glycerol trioleate and glycerol trierucate (Lorenzo’s oil), bone marrow transplantation, and lovastatin (see Chapter 599.3).

Bibliography is available at Expert Consult.

575.2 Secondary and Tertiary Adrenal Insufficiency
Perrin C. White

ETIOLOGY
Abrupt Cessation of Administration of Corticosteroids

Secondary adrenal insufficiency most commonly occurs when the hypothalamic-pituitary-adrenal axis is suppressed by prolonged administration of high doses of a potent glucocorticoid and that agent is suddenly withdrawn or the dose is tapered too quickly. Patients at risk for this problem include those with leukemia, asthma (particularly when patients are transitioned from oral to inhaled corticosteroids), and collagen vascular disease or other autoimmune conditions and those who have undergone tissue transplants or neurosurgical procedures. The maximal duration and dosage of glucocorticoid that can be administered before encountering this problem is not known, but it is assumed that high-dose glucocorticoids (the equivalent of >10 times physiologic cortisol secretion) can be administered for at least 1 wk without requiring a subsequent taper of dose. On the other hand, when high doses of dexamethasone are given to children with leukemia, it can take up to 2 mo or longer after therapy is stopped before tests of adrenal function return to normal. Signs and symptoms of adrenal insufficiency are most likely in patients who are subsequently subjected to stresses such as severe infections or additional surgical procedures.

Corticotropin (Adrenocorticotropic Hormone) Deficiency

Pituitary or hypothalamic dysfunction can cause corticotropin deficiency (see Chapter 557), usually associated with deficiencies of other pituitary hormones such as growth hormone and thyrotropin. Destructive lesions in the area of the pituitary, such as craniopharyngioma and germinoma, are the most common causes of corticotropin deficiency. In many cases, the pituitary or hypothalamus is further damaged during surgical removal or radiotherapy of tumors in the midline of the brain. Traumatic brain injury (see Chapter 710) frequently causes pituitary dysfunction, especially in the first days after the injury. However, corticotropin deficiency is difficult to detect then owing to frequent use of high doses of dexamethasone to minimize brain swelling, and permanent corticotropin deficiency is unusual after traumatic brain injury. In rare instances, autoimmune hypophysitis is the cause of corticotropin deficiency.

Congenital lesions of the pituitary also occur. The pituitary alone may be affected, or additional midline structures may be involved, such as the optic nerves or septum pellucidum. The latter type of abnormality is termed septooptic dysplasia, or de Morsier syndrome (see Chapter 591.9). More-severe developmental anomalies of the brain, such as anencephaly and holoprosencephaly, can also affect the pituitary. These disorders are usually sporadic, although a few cases of autosomal recessive inheritance have occurred. Isolated deficiency of corticotropin has been reported, including in several sets of siblings. Patients with multiple pituitary hormone deficiencies caused by mutations in the PRO1 gene have been described with progressive ACTH/cortisol deficiency. Isolated deficiency of corticotropin-releasing hormone has been documented in an Arab kindred as an autosomal recessive trait.

It was recently recognized that up to 60% of children with Prader-Willi syndrome (see Chapter 81.8) have some degree of secondary adrenal insufficiency as assessed by provocative testing with metyrapone (see “Laboratory Findings” in Chapter 575.2), although diurnal cortisol levels are normal. The clinical significance of this finding is uncertain, but it might contribute to the relatively high incidence of sudden death with infectious illness that occurs in this population. Although it is not yet a standard of care, some endocrinologists advocate treating patients who have Prader-Willi syndrome with hydrocortisone during febrile illness.

CLINICAL PRESENTATION

Aldosterone secretion is unaffected in secondary adrenal insufficiency because the adrenal gland is, by definition, intact and the renin-angiotensin system is not involved. Thus, signs and symptoms are those of cortisol deficiency. Newborns often have hypoglycemia. Older children can have orthostatic hypotension or weakness. Hyponatremia may be present.

When secondary adrenal insufficiency is the consequence of an inborn or acquired anatomic defect involving the pituitary, there may be signs of associated deficiencies of other pituitary hormones. The penis may be small in male infants if gonadotropins are also deficient. Infants with secondary hypothyroidism are often jaundiced. Children with associated growth hormone deficiency grow poorly after the 1st yr of life.

Some children with pituitary abnormalities have hypoplasia of the midface. Children with optic nerve hypoplasia can have obvious visual impairment. They usually have a characteristic wandering nystagmus, but this is often not apparent until several months of age.

LABORATORY FINDINGS

Because the adrenal glands themselves are not directly affected, the diagnosis of secondary adrenal insufficiency is sometimes challenging. Historical gold standard dynamic tests include insulin-induced hypoglycemia, which provides a potent stress to the entire hypothalamic-pituitary-adrenal (HPA) axis. This test requires constant attendance by a physician and is considered by many endocrinologists to be too dangerous for routine use. A second gold standard test uses metyrapone, a specific inhibitor of steroid 11β-hydroxylase (CYP11B1) to
Bibliography


block cortisol synthesis, thus removing the normal negative feedback of cortisol on ACTH secretion. There are several protocols for this test; one version administers 30 mg/kg of metyrapone orally at midnight, with a blood sample obtained for cortisol and 11-deoxycortisol (the substrate for 11β-hydroxylase) at 8 AM. A low cortisol level (<5 µg/dL) demonstrates adequate suppression of cortisol synthesis, and an 11-deoxycortisol level >7 µg/dL indicates that ACTH has responded normally to the cortisol deficiency by stimulating the adrenal cortex. This test should be used with caution outside the research setting because it can precipitate adrenal crises in patients with marginal adrenal function; the drug is not available in all locales.

At present, the most commonly used test to diagnose secondary adrenal insufficiency is low-dose ACTH stimulation testing (1 µg/1.73 m² of cosyntropin given intravenously), the rationale being that there will be some degree of atrophy of the adrenal cortex if normal physiologic ACTH stimulation is lacking. Thus, this test may be falsely negative in cases of acute compromise of the pituitary (e.g., injury or surgery). Such circumstances rarely pose a diagnostic dilemma; in general, this test provides excellent sensitivity and specificity. Although assays vary somewhat, a threshold cortisol level of 18-20 µg/dL 30 min after cosyntropin administration may be used to dichotomize normal and abnormal responses.

At present, there seems to be little reason to use stimulation with corticotropin-releasing hormone instead of ACTH; although the corticotropin-releasing hormone test has the theoretical advantage of testing the ability of the anterior pituitary to respond to this stimulus by secreting ACTH (thus distinguishing secondary and tertiary adrenal insufficiency), in practice it does not provide improved sensitivity and specificity, and the agent is not as widely available.

**TREATMENT**

Iatrogenic secondary adrenal insufficiency (caused by chronic glucocorticoid administration) is best avoided by use of the smallest effective doses of systemic glucocorticoids for the shortest period of time. When a patient is thought to be at risk, tapering the dose rapidly to a level equivalent to or slightly less than the physiologic replacement dose (~10 mg/m²/24 hr of hydrocortisone) and further tapering over several weeks can allow the adrenal cortex to recover without development of signs of adrenal insufficiency. Patients with anatomic lesions of the pituitary should be treated indefinitely with glucocorticoids. Mineralocorticoid replacement is not required. In patients with panhypopituitarism, treating cortisol deficiency can increase free water excretion, thus unmasking central diabetes insipidus. Electrolytes must be monitored carefully when initiating cortisol therapy in panhypopituitary patients.

Bibliography is available at Expert Consult.

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**575.3 Adrenal Insufficiency in the Critical Care Setting**

**Perrin C. White**

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**ETIOLOGY**

Adrenal insufficiency in the context of critical illness is encountered in up to 20-50% of pediatric patients, often as a transient condition. In many cases, it is considered to be “functional” or “relative” in nature, meaning that cortisol levels are within normal limits but cannot increase sufficiently to meet the demands of critical illness. The causes are heterogeneous, and some were discussed in Chapter 575.1. They include adrenal hypoperfusion from shock, particularly septic shock, as is often seen in meningococcemia. Inflammatory mediators during septic shock, particularly interleukin-6, can suppress ACTH secretion, directly suppress cortisol secretion, or both. Elomitrile, used as sedation for intubation, inhibits steroid 11β-hydroxylase and thus blocks cortisol biosynthesis. Neurosurgical patients with closed head trauma, or with tumors that involve the hypothalamus or pituitary, might have ACTH deficiency in the context of panhypopituitarism. Some children have been previously treated with systemic corticosteroids (e.g., children with leukemia) and have suppression of the HPA axis for that reason. In the intensive care nursery, premature infants have not yet developed normal cortisol biosynthetic capacity (see Chapter 574.2) and thus may not be able to secrete adequate amounts of this hormone when ill.

**CLINICAL MANIFESTATIONS**

Cortisol is required for catecholamines to have their normal pressor effects on the cardiovascular system (see Chapters 574.4 and 574.5). Accordingly, adrenal insufficiency is often suspected in hypotensive patients who do not respond to intravenous pressor agents. Patients may be at increased risk for hypoglycemia or a presentation resembling the syndrome of inappropriate antidiuretic hormone secretion, but these conditions commonly occur in the context of sepsis, and the contribution of adrenal insufficiency may be difficult to distinguish.

**LABORATORY FINDINGS**

Although low random cortisol levels in severely stressed patients are certainly abnormal, very high levels are also associated with a poor outcome in such patients; the latter situation presumably reflects a maximally stimulated adrenal cortex with diminished reserve. ACTH (cosyntropin) stimulation testing is generally considered the best way to diagnose adrenal insufficiency in this setting (see Chapter 575.1); evidence suggests that the low-dose (1 µg/1.73 m²) test may be superior to the 250 µg standard dose test, although this remains controversial. Generally, a peak cortisol level <18 µg/dL or an increment of <9 µg/dL from baseline is considered suggestive for adrenal insufficiency in this context. In evaluating cortisol levels, it should be remembered that cortisol in the circulation is normally mostly bound to cortisol-binding globulin; in hypoproteinemic states total cortisol levels may be decreased, whereas free cortisol levels might be normal. It may be prudent to measure free cortisol before initiating treatment when total cortisol is low and albumin is <2.5 g/dL, but such measurements are not readily available in all institutions.

**TREATMENT**

There are limited data regarding treatment efficacy in critically ill children. Based on studies of both children and adults, it is likely that moderate stress doses of hydrocortisone (e.g., 50 mg/m²/day) improve responses to pressor agents in patients with shock and documented adrenal insufficiency. It is uncertain if there is a beneficial effect on overall survival. There seems to be no benefit in using pharmacologic doses of potent synthetic glucocorticoids such as dexamethasone.

Bibliography is available at Expert Consult.

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**575.4 Altered End-Organ Sensitivity to Corticosteroids**

**Perrin C. White**

Diseases can result from altered actions of hormones at their physiologic targets. These may be caused by abnormal metabolism of hormones, mutations in hormone receptors, or defects in cellular effectors (such as ion channels) that are targets of hormone action.

**GENERALIZED GLUCOCORTICOID RESISTANCE**

**Etiology**

Patients with generalized glucocorticoid resistance have target-tissue insensitivity to glucocorticoids. The condition is usually inherited in an autosomal dominant manner but sporadic cases occur. Impairment of normal negative feedback of cortisol at the levels of the hypothalamus and pituitary activates the HPA axis with consequent increases in ACTH and cortisol concentrations. Generalized glucocorticoid resistance is caused by mutations in the glucocorticoid receptor (encoded
Bibliography
Bibliography


isoyme converts cortisol to an inactive metabolite, cortisone; the 2 steroids differ in the presence of an 11β-hydroxyl vs an 11-oxo group, respectively. Mutations in this enzyme cause the syndrome of **apparent mineralocorticoid excess**. Conversely, the 11-HSD1 isozyme converts cortisone to cortisol, and so it is sometimes referred to as “cortisone reductase.” This isozyme is expressed at high levels in glucocorticoid target tissues, particularly the liver, where it ensures adequate levels of active glucocorticoids (cortisol and corticosterone) to meet metabolic demands without requiring excessive adrenal cortisol secretion.

The 11-HSD1 isozyme is located in the endoplasmic reticulum (i.e., it is a “microsomal” enzyme) and functions as a dimer. It accepts electrons from reduced nicotine–adenine dinucleotide phosphate, which is generated within the endoplasmic reticulum by hexose-6-phosphate dehydrogenase, an enzyme distinct from cytoplasmic glucose-6-phosphate dehydrogenase.

Apparent cortisone reductase deficiency is caused by homozygous mutations in hexose-6-phosphate dehydrogenase that prevent generation of reduced nicotine–adenine dinucleotide phosphate within the endoplasmic reticulum and thus starve 11-HSD1 of its essential cofactor for the reductase reaction. Very rare patients have been reported to have heterozygous mutations in the HSD11B1 gene encoding 11-HSD1 itself and thus have “true” cortisone reductase deficiency; because the enzyme functions as a homodimer, heterozygous mutations are able to impair three fourths of all dimmers.

### Laboratory Findings

The ratio of cortisol to cortisone in blood is lower than usual. The same is true of urinary metabolites, typically measured as a ratio of the sum of the tetrahydrocortisol and allo-tetrahydrocortisol excretion to that of tetrahydrocortisone. These determinations are best accomplished by gas chromatography followed by mass spectrometry, and are available in specialized reference laboratories. Absolute levels of cortisol and ACTH are within normal limits.

### Differential Diagnosis

Cortisone reductase deficiency has to be distinguished from, and is much less common than, other causes of androgen excess such as polycystic ovarian syndrome and nonclassical congenital adrenal hyperplasia as a result of 21-hydroxylase deficiency.

### Treatment

Treatment is aimed at decreasing adrenal overactivity and thus reducing secretion of androgens. This can be accomplished by administration of hydrocortisone.

### ALTERED END-ORGAN SENSITIVITY TO MINERALOCORTICOIDS

#### Pseudohypoaldosteronism

**Etiology**

Pseudohypoaldosteronism type 1 (PHA1) is a monogenic disease in which aldosterone action is deficient and patients are thus unable to resorb urinary sodium or excrete potassium properly. There are 2 forms. A relatively mild **autosomal dominant** form is caused by mutations in the NR3C2 gene encoding the human mineralocorticoid receptor. As with generalized glucocorticoid resistance, a heterozygous mutation is sufficient to cause disease because the
mineralocorticoid receptor interacts with DNA as a dimer, and three fourths of the dimers are defective in individuals carrying heterozygous mutations (assuming mutant protein is synthesized). A more severe autosomal recessive form is usually the result of homozygous mutations in the α (SCNN1A), β (SCNN1B), or γ (SCNN1G) subunits of the epithelial Na(+) channel, but 1 reported case of severe autosomal recessive disease was caused by homozygous mutations in NR3C2.

PHA1 should not be confused with pseudohypoaldosteronism type 2, a rare mendelian syndrome characterized by hyperkalemia and, in contrast to PHA1, by hypertension from excessive renal salt reabsorption. This disorder is caused by mutations in the renal regulatory kinases, WNK1 and WNK4, or components of an E3 ubiquitin ligase complex Kelch-like 3 (KLHL3) and Cullin 3 (CUL3).

### Clinical Manifestations
Infants with PHA1 present with hyperkalemia, hypotension, and failure to thrive. In more-severe (usually autosomal recessive) cases, salt loss is not confined to the kidney but instead occurs from most epithelia. Mothers may report that the skin of their affected infants tastes salty. Some infants suffer from cystic fibrosis–like pulmonary symptoms. It is often difficult to control electrolyte abnormalities in patients with the autosomal recessive form, leading to frequent hospitalizations and a need for close clinical monitoring.

It is noteworthy that signs and symptoms of aldosterone deficiency tend to remit as the patients get older, particularly in the autosomal dominant form. This is similar to what is seen in actual aldosterone deficiency as occurs in the salt-losing forms of congenital adrenal hyperplasia or aldosterone synthase deficiency. The kidney matures after early infancy to become more efficient at excreting potassium, and whereas breast milk and infant formula are low in sodium, the normal adult Western diet is relatively high in sodium, thus compensating for the renal salt wasting.

### Laboratory Findings
Infants have marked hyperkalemia and hypotension. Both plasma renin and aldosterone are markedly elevated. Levels of cortisol and ACTH are normal. If hypovolemia is severe, patients may develop prerenal azotemia. The electrocardiogram may include tall peaked T waves with severe hyperkalemia or ventricular tachycardia.

### Differential Diagnosis
PHA in infants should be distinguished from other causes of hyperkalemia and hypotension. These include renal failure of any cause, congenital adrenal hyperplasia, aldosterone synthase deficiency, and other causes of adrenocortical insufficiency such as AHC. Patients with renal failure will have elevated blood urea nitrogen and creatinine, but these may be seen in severely dehydrated patients with PHA. Patients with any form of adrenal insufficiency in this clinical context will have low or low-normal aldosterone levels (with elevated plasma renin), in contrast to the elevated aldosterone levels seen in PHA. Patients with congenital adrenal hyperplasia have elevated levels of steroid precursors such as 17-hydroxyprogesterone (in patients with 21-hydroxylase deficiency), and patients with most forms of adrenal insufficiency have elevated ACTH levels.

### Treatment
Infants must be given dietary sodium supplementation (initially intravenous and then oral), typically approximately 8 mEq/kg/day. Potassium levels in the infant formula often need to be reduced, which may be accomplished by mixing the formula with polysyrone resin (Kayexalate) and then decanting the formula prior to feeding. Fluorocortisone, a synthetic mineralocorticoid, may be efficacious in milder autosomal dominant cases if administered in high doses (titrating up to ~0.5 mg daily). Significant electrolyte abnormalities require treatment with intravenous normal saline and rectal polysyrone resin. Severe hyperkalemia may require glucose and insulin infusions to control.

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**APPARENT MINERALOCORTICOID EXCESS**

### Etiology
The syndrome of apparent mineralocorticoid excess is an autosomal recessive disorder caused by mutations in the HSD11B2 gene encoding the 11-HSD2 isozyme of 11β-hydroxysteroid dehydrogenase. The mineralocorticoid receptor actually has nearly identical affinities for aldosterone (the main mineralocorticoid hormone) and cortisol, yet cortisol is normally only a weak mineralocorticoid in vivo. This is because 11-HSD2 is expressed along with the mineralocorticoid receptor in most target tissues such as the renal cortical collecting duct epithelium. It converts cortisol to cortisone, which is not an active steroid, thus preventing it from occupying the mineralocorticoid receptor. In contrast, aldosterone is not a substrate for the enzyme because its 11β-hydroxyl group forms a hemiketal with the 18-aldehyde group of the steroid and is thus not accessible to the enzyme. Thus, in the absence of 11-HSD2, cortisol is able to efficiently occupy the mineralocorticoid receptor, and because cortisol concentrations are normally far higher than those of aldosterone, this results in signs and symptoms of mineralocorticoid excess.

A similar clinical picture occurs with excessive consumption of licorice or licorice-flavored chewing tobacco; licorice contains compounds including glycyrrhetinic and glycyrrhizic acids that inhibit 11-HSD2. Carbenoxolone, an antihypertensive drug that is not marketed in the United States, has similar effects.

### Clinical Manifestations
Affected infants often have some degree of intrauterine growth restriction with birth weights of 2 kg typical for term infants. Infants and children often fail to thrive. Severe hypertension (to ~200/120 mm Hg) is almost always present. In some patients, the hypertension tends to be labile or paroxysmal with severe emotional stress as a precipitating factor. Complications of hypertension have included cerebrovascular accidents. Several patients have died during infancy or adolescence, either from electrolyte imbalances leading to cardiac arrhythmias or from vascular sequelae of hypertension. Hypokalemic alkalosis can eventually cause nephrocalcinosis (often visible on renal ultrasound) and nephrogenic diabetes insipidus leading to polyuria and polydipsia. Deleterious effects on muscle range from elevations in serum creatine phosphokinase to frank rhabdomyolysis. Electrocardiograms show left ventricular hypertrophy.

### Laboratory Findings
Hypokalemia and alkalosis are common but not persistent. Sodium levels are generally in the upper part of the reference range. Aldosterone and renin levels are very low because the hypertension and hypervolemia are independent of aldosterone concentrations. Serum cortisol and ACTH levels are generally within normal limits. The serum half-life of cortisol is increased, but the test for this requires a radioactive tracer and is not clinically available. Total urinary excretion of cortisol metabolites is markedly decreased. The urinary ratio of free cortisol to free cortisone is elevated, as is the ratio of urinary tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone.

### Differential Diagnosis
The differential diagnosis includes other forms of severe childhood hypertension such as renal artery anomalies, but relatively few conditions present with suppressed renin and aldosterone levels. Liddle syndrome has a similar presentation but no abnormalities in the steroid profile, typically has an autosomal dominant mode of inheritance, and does not respond to treatment with mineralocorticoid receptor antagonists. Hypertensive forms of congenital adrenal hyperplasia (see Chapter 576) also have suppressed renin and aldosterone levels, but they present with signs of androgen excess (11β-hydroxylase deficiency) or androgen deficiency (17α-hydroxylase deficiency); the latter can be difficult to appreciate in young children. The steroid profiles in congenital adrenal hyperplasia differ from those seen in apparent mineralocorticoid excess syndrome.

Patients with severe Cushing syndrome may have high enough cortisol levels to overwhelm renal 11-HSD2, leading to severe
hypertension with alterations in urinary cortisol-to-cortisone ratios. This occurs most often in patients with the ectopic ACTH syndrome. This generally does not present a diagnostic dilemma, because of the other signs of Cushing syndrome including high cortisol levels.

**Treatment**
Treatment includes a low-salt diet, potassium supplementation, and mineralocorticoid receptor blockade with spironolactone or eplerene; a sodium channel blocker, such as amiloride or triamterene may work at least as well. In principle, suppression of cortisol secretion with dexamethasone (which does not bind the mineralocorticoid receptor) should work, but in practice it is much less effective than mineralocorticoid receptor blockade.

**LIDDLE SYNDROME**

**Etiology**
Liddle syndrome is a form of hypertension and hypokalemia that is clinically similar to the syndrome of apparent mineralocorticoid excess, but it is inherited in an autosomal dominant manner. It is caused by activating mutations in the β (SCNN1B) or γ (SCNN1G) subunits of the epithelial sodium channel. Most of these mutations prevent the channel subunits from being ligated to ubiquitin and targeted to the proteosome for degradation, a process that is normally regulated indirectly by aldosterone. The net effect is to increase the number of open channels at the apical surface of epithelial cells of the renal collecting duct, thus facilitating sodium resorption and potassium excretion. This disorder is thus the exact opposite of the autosomal recessive form of pseudohypoaldosteronism discussed previously.

**Clinical Manifestations, Laboratory Findings, and Differential Diagnosis**
Liddle syndrome is characterized by severe early-onset hypertension and by hypokalemia, which may not be persistent. Aldosterone and renin levels are suppressed but all steroid hormone levels are normal.

The differential diagnosis is the same as that for apparent mineralocorticoid excess.

**Treatment**
The mainstays of treatment are a low-salt diet, potassium supplementation, and a sodium channel blocker such as amiloride or triamterene. Mineralocorticoid receptor antagonists such as spironolactone are ineffective.

_Bibliography is available at Expert Consult._
Generalized Glucocorticoid Resistance

Cortisone Reductase Deficiency

Altered End-Organ Sensitivity to Mineralocorticoids

Apparent Mineralocorticoid Excess

Liddle Syndrome
Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis (normal adrenal steroidogenesis is discussed in Chapter 574). Cortisol deficiency increases secretion of corticotropin (adrenocorticotropic hormone [ACTH]), which, in turn, leads to adrenocortical hyperplasia and overproduction of intermediate metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or precocious puberty in affected males; and virilization or sexual infantilism in affected females (Figs. 576-1 and 576-2 and Table 576-1).

576.1 Congenital Adrenal Hyperplasia Caused by 21-Hydroxylase Deficiency

**ETIOLOGY**

More than 90% of CAH cases are caused by 21-hydroxylase deficiency. This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively (see Fig. 574-1 in Chapter 574). These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most-severe, "salt-wasting" form of the disease. Slightly less-severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed "simple virilizing disease". These 2 forms are collectively termed classic 21-hydroxylase deficiency. Patients with nonclassic disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth. Clinical presentation is dependent, in part, on the genotype (see below, "Genetics") (Table 576-2).

**EPIDEMIOLOGY**

Classic 21-hydroxylase deficiency occurs in approximately 1 in 15,000-20,000 births in most populations. Approximately 70% of affected infants have the salt-losing form, whereas 30% have the simple virilizing form of the disorder. In the United States, CAH is less common in African-Americans compared with white children (1:42,000 vs 1:15,500). Nonclassic disease has a prevalence of approximately 1 in 1,000 in the general population, but occurs more frequently in specific ethnic groups such as Ashkenazi Jews and Hispanics.

**GENETICS**

There are 2 steroid 21-hydroxylase genes—CYP21P (CYP21A1P, CYP21A) and CYP21 (CYP21A2, CYP21B)—which alternate in tandem with 2 genes for the fourth component of complement (C4A and C4B) in the human leukocyte antigen (HLA) major histocompatibility complex on chromosome 6p21.3 between the HLA-B and HLA-DR loci. Many other genes are located in this cluster. CYP21 is the active gene; CYP21P is 98% identical in DNA sequence to CYP21 but is a pseudogene because of 9 different mutations. More than 90% of mutations causing 21-hydroxylase deficiency are recombinations between CYP21 and CYP21P. Approximately 20% are deletions generated by unequal meiotic crossing-over between CYP21 and CYP21P, whereas the remainder are nonreciprocal transfers of deleterious mutations from CYP21P to CYP21, a phenomenon termed gene conversion.

The deleterious mutations in CYP21P have different effects on enzymatic activity when transferred to CYP21. Several mutations completely prevent synthesis of a functional protein, whereas others are missense mutations (they result in amino acid substitutions) that yield enzymes with 1-50% of normal activity. Disease severity correlates well with the mutations carried by an affected individual; for example, patients with salt-wasting disease usually carry mutations on both alleles that completely destroy enzymatic activity. Patients are frequently compound heterozygotes for different types of mutations (i.e., 1 allele is less-severely affected than the other), in which case the severity of disease expression is largely determined by the activity of the less-severely affected of the 2 alleles.

Closely adjacent to, but on the opposite DNA strand from, CYP21 is the tenascin-X (TNX) gene, which encodes a connective tissue protein. Rarely, deletions of CYP21 extend into TNX. Such patients may have a contiguous gene syndrome (see Chapter 81.1) consisting of CAH and Ehlers-Danlos syndrome (see Chapters 484 and 659).
Figure 576-1 A, A 6-yr-old girl with congenital virilizing adrenal hyperplasia. The height age was 8.5 yr, and the bone age was 13 yr. B, Notice the clitoral enlargement and labial fusion. C, Her 5 yr old brother was not considered to be abnormal by the parents. The height age was 8 yr, and the bone age was 12.5 yr.

Figure 576-2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants A and B had the salt-wasting form and received the diagnosis early in infancy. Infant C was referred at 1 yr of age because of bilateral cryptorchidism. Notice the completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>AFFECTED GENE AND CHROMOSOME</th>
<th>SIGNS AND SYMPTOMS</th>
<th>LABORATORY FINDINGS</th>
<th>THERAPEUTIC MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-Hydroxylase deficiency, classic form</td>
<td>CYP21 6p21.3</td>
<td>Glucocorticoid deficiency</td>
<td>↓ Cortisol, ↑ ACTH</td>
<td>Glucocorticoid (hydrocortisone) replacement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mineralocorticoid deficiency (salt-wasting crisis)</td>
<td>↑↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous genitalia in females</td>
<td>Hyponatremia, hyperkalemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postnatal virilization in males and females</td>
<td>↑ Plasma renin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Serum androgens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Serum androgens</td>
<td></td>
</tr>
<tr>
<td>21-Hydroxylase deficiency, nonclassic form</td>
<td>CYP21 6p21.3</td>
<td>May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility</td>
<td>↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone</td>
<td>Suppression with glucocorticoids</td>
</tr>
<tr>
<td>11β-Hydroxylase deficiency</td>
<td>CYP11B1 8q24.3</td>
<td>Glucocorticoid deficiency</td>
<td>↓ Cortisol, ↑ ACTH</td>
<td>Glucocorticoid (hydrocortisone) replacement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mineralocorticoid deficiency (salt-wasting crisis)</td>
<td>↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous genitalia in females</td>
<td>↑ Serum androgens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postnatal virilization in males and females</td>
<td>↓ Serum androgens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Plasma renin</td>
<td></td>
</tr>
<tr>
<td>3β-Hydroxysteroid dehydrogenase deficiency, classic form</td>
<td>HSD3B2 1p13.1</td>
<td>Glucocorticoid deficiency</td>
<td>↓ Cortisol, ↑ ACTH</td>
<td>Glucocorticoid (hydrocortisone) replacement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mineralocorticoid deficiency (salt-wasting crisis)</td>
<td>↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxy-pregnenolone, DHEA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous genitalia in females</td>
<td>Hyponatremia, hyperkalemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postnatal virilization in males and females</td>
<td>↑ Plasma renin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ DHEA, ↓ androstenedione, testosterone, and estradiol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precocious adrenarche, disordered puberty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17α-Hydroxylase/17,20-lyase deficiency</td>
<td>CYP17 10q24.3</td>
<td>Cortisol deficiency (corticosterone is an adequate glucocorticoid)</td>
<td>↓ Cortisol, ↑ ACTH</td>
<td>Glucocorticoid (hydrocortisone) administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous genitalia in males</td>
<td>↑ DOC, corticosterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sexual infantilism</td>
<td>Low 17α-hydroxylated steroids; poor response to ACTH</td>
<td>Orchiopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
<td>↓ Serum androgens; poor response to hCG</td>
<td>Sex hormone replacement consonant with sex of rearing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Plasma androgens or estrogens</td>
<td>Suppression with glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Plasma renin; hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Congenital lipoid adrenal hyperplasia</td>
<td>STAR 8p11.2</td>
<td>Glucocorticoid deficiency</td>
<td>↑ ACTH</td>
<td>Glucocorticoid (hydrocortisone) replacement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mineralocorticoid deficiency (salt-wasting crisis)</td>
<td>Low levels of all steroid hormones, with decreased or absent response to ACTH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous genitalia in males</td>
<td>Hyponatremia, hyperkalemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor pubertal development or premature ovarian failure in females</td>
<td>↓ Aldosterone, ↑ plasma renin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased or absent response to hCG in males</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ FSH, ↑ LH, ↓ estradiol (after puberty)</td>
<td>Estrogen replacement</td>
</tr>
</tbody>
</table>
Table 576-1  Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont’d

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>AFFECTED GENE AND CHROMOSOME</th>
<th>SIGNS AND SYMPTOMS</th>
<th>LABORATORY FINDINGS</th>
<th>THERAPEUTIC MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>P450 21-</td>
<td>oxidoreductase deficiency</td>
<td>POR 7q11.3</td>
<td>Glucocorticoid deficiency</td>
<td>↓ Cortisol, ↑ ACTH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ambiguous genitalia in males and females</td>
<td>↑ Pregnenolone, ↑ progesterone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal virilization Antley-Bixler syndrome</td>
<td>↑ Serum androgens prenatally, ↓ estrogens to androgens</td>
</tr>
</tbody>
</table>

↓ Decreased; ↑, increased; ††, markedly increased; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table 576-2  Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

<table>
<thead>
<tr>
<th>MUTATION GROUP</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic activity, % normal</td>
<td>Nil</td>
<td>1-2%</td>
<td>20-50%</td>
</tr>
<tr>
<td>CYP21 mutations (phenotype generally corresponds to the least affected allele)</td>
<td>Gene deletion</td>
<td>I172N</td>
<td>P30L</td>
</tr>
<tr>
<td></td>
<td>Exon 3 del 8 bp</td>
<td></td>
<td>V281L</td>
</tr>
<tr>
<td></td>
<td>Exon 6 cluster</td>
<td></td>
<td>P453S</td>
</tr>
<tr>
<td></td>
<td>Q318X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R356W</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intron 2 splice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Salt wasting</td>
<td>Simple virilizing</td>
<td>Nonclassic</td>
</tr>
<tr>
<td>Aldosterone synthesis</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Age at diagnosis (without newborn screening)</td>
<td>Infancy</td>
<td>Infancy (females)</td>
<td>Childhood to adulthood, or asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Childhood (males)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virilization</td>
<td>Severe</td>
<td>Moderate to severe</td>
<td>None to Mild</td>
</tr>
<tr>
<td>Incidence</td>
<td>1/20,000</td>
<td>1/50,000</td>
<td>1/500</td>
</tr>
</tbody>
</table>

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Aldosterone and Cortisol Deficiency

Because both cortisol and aldosterone require 21-hydroxylation for their synthesis, both hormones are deficient in the most-severe, salt-wasting form of the disease. This form constitutes approximately 70% of cases of classic 21-hydroxylase deficiency. The signs and symptoms of cortisol and aldosterone deficiency, and the pathophysiology underlying them, are essentially those described in Chapter 575. These include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, and hyperkalemia. These problems typically first develop in affected infants at approximately 10-14 days of age. Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks.

CAH differs from other causes of primary adrenal insufficiency in that precursor steroids accumulate proximal to the blocked enzymatic conversion. Because cortisol is not synthesized efficiently, ACTH levels are high, leading to hyperplasia of the adrenal cortex and levels of precursor steroids that may be hundreds of times normal. In the case of 21-hydroxylase deficiency, these precursors include 17-hydroxyprogesterone and progesterone. Progesterone and perhaps other metabolites act as antagonists of the mineralocorticoid receptor and thus may exacerbate the effects of aldosterone deficiency in untreated patients.

Prenatal Androgen Excess

The most important problem caused by accumulation of steroid precursors is that 17-hydroxyprogesterone is shunted into the pathway for androgen biosynthesis, leading to high levels of androstenedione that are converted outside the adrenal gland to testosterone. This problem begins in affected fetuses by 8-10 wk of gestation and leads to abnormal genital development in females (see Figs. 576-1 and 576-2).

The external genitalia of males and females normally appear identical early in gestation (see Chapter 582). Affected females who are exposed in utero to high levels of androgens of adrenal origin have masculinized external genitalia (see Figs. 576-1 and 576-2). This is manifested by enlargement of the clitoris and by partial or complete labial fusion. The vagina usually has a common opening with the urethra (urogenital sinus). The clitoris may be so enlarged that it resembles a penis; because the urethra opens below this organ, some affected females may be mistakenly presumed to be males with hypoplasia and cryptorchidism. The severity of virilization is usually greatest in females with the salt-losing form of 21-hydroxylase deficiency (see Table 576-2). The internal genital organs are normal, because affected females have normal ovaries and not testes and thus do not secrete antimüllerian hormone.

Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females. Girls may demonstrate aggressive play behavior, tend to be interested in masculine toys such as cars and trucks, and often show decreased interest in playing with dolls. Women may have decreased interest in maternal roles. There is an increased frequency of homosexuality in affected females. Nonetheless, most function heterosexually and do not have gender identity confusion or dysphoria. It is unusual for affected females to assign themselves a male role except in some with the severest degree of virilization.

Male infants appear normal at birth. Thus, the diagnosis may not be made in boys until signs of adrenal insufficiency develop. Because
patients with this condition can deteriorate quickly, infant boys are more likely to die than infant girls. For this reason, all 50 American states and many countries have instituted newborn screening for this condition (see “Newborn Screening” in Chapter 576.2).

Postnatal Androgen Excess
Unattended or inadequately treated children of both sexes develop additional signs of androgen excess after birth. Boys with the simple virilizing form of 21-hydroxylase deficiency often have a delayed diagnosis because they appear normal and rarely develop adrenal insufficiency.

Signs of androgen excess include rapid somatic growth and accelerated skeletal maturation. Thus, affected patients are tall in childhood but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted (see Fig. 576-1). Muscular development may be excessive. Pubic and axillary hair may appear, and acne and a deep voice may develop. The penis, scrotum, and prostate may become enlarged in affected boys; however, the testes are usually prepubertal in size so that they appear relatively small in contrast to the enlarged penis. Occasionally, ectopic adrenocortical cells in the testes of patients become hyperplastic similarly to the adrenal glands, producing testicular adrenal rest tumors (see Chapter 584). The clitoris may become further enlarged in affected females (see Fig. 576-1). Although the internal genital structures are female, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.

Similar but usually milder signs of androgen excess may occur in nonclassic 21-hydroxylase deficiency (see Table 576-2). In this attenuated form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth. Males and females may present with precocious puberty and early development of pubic and axillary hair. Hirsutism, acne, menstrual disorders, and infertility may develop later in life, but many females and males are completely asymptomatic.

Adrenomedullary Dysfunction
Development of the adrenal medulla requires exposure to the extremely high cortisol levels normally present within the adrenal gland. Thus patients with classic CAH have abnormal adrenomedullary function, as evidenced by blunted epinephrine responses, decreased blood glucose, and lower heart rates with exercise. Ability to exercise is unimpaired and the clinical significance of these findings is uncertain. Adrenomedullary dysfunction may exacerbate the cardiovascular effects of cortisol deficiency in untreated or undertreated patients.

LABORATORY FINDINGS
See Table 576-1.

Patients with salt-losing disease have typical laboratory findings associated with cortisol and aldosterone deficiency, including hypotension, hyperkalemia, metabolic acidosis, and, often, hypoglycemia, but these abnormalities can take 10-14 days or longer to develop after birth. Blood levels of 17-hydroxyprogesterone are markedly elevated. However, levels of this hormone are high during the 1st 2-3 days of life even in unaffected infants and especially if they are sick or premature. After infancy, once the circadian rhythm of cortisol is established, 17-hydroxyprogesterone levels vary in the same circadian pattern, being highest in the morning and lowest at night. Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels. In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females; testosterone is not elevated in affected males, because normal infant males have high testosterone levels compared with those seen later in childhood. Levels of urinary 17-ketosteroids and pregnanetriol are elevated but are now rarely used clinically because blood samples are easier to obtain than 24-hr urine collections. ACTH levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level. However, renin levels are high in normal infants in the 1st few wk of life.

Diagnosis of 21-hydroxylase deficiency is most reliably established by measuring 17-hydroxyprogesterone before and 30 or 60 min after an intravenous bolus of 0.125-0.25 mg of cosyntropin (ACTH 1-24). Nomograms exist that readily distinguish normals and patients with nonclassic and classic 21-hydroxylase deficiency. Heterozygous carriers of this autosomal recessive disorder tend to have higher ACTH-stimulated 17-hydroxyprogesterone levels than genetically unaffected individuals, but there is significant overlap between subjects in these 2 categories. However, in infants with frank electrolyte abnormalities or circulatory instability, it may not be possible or necessary to delay treatment to perform this test, as levels of precursors will be sufficiently elevated on a random blood sample to make the diagnosis.

Genotyping is clinically available and may help confirm the diagnosis, but it is expensive and may take weeks. Because the gene conversions that generate most mutant alleles may transfer more than one mutation, at least one parent should be genotyped as well to determine which mutations lie on each allele.

DIFFERENTIAL DIAGNOSIS
Disorders of sexual development are discussed more generally in Chapter 588. The initial step in evaluating an infant with ambiguous genitals is a thorough physical examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads almost always indicate the presence of testicular tissue and thus that the infant is a genetic male), and look for any other anatomic abnormalities. Ultrasonography is helpful in demonstrating the presence or absence of a uterus and can often locate the gonads. A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant. These results are all likely to be available before the results of hormonal testing and together allow the clinical team to advise the parents as to the genetic sex of the infant and the anatomy of internal reproductive structures. Injection of contrast medium into the urogenital sinus of a virilized female demonstrates a vagina and uterus, and many surgeons utilize this information to formulate a plan for surgical management.

PRENATAL DIAGNOSIS
Prenatal diagnosis of 21-hydroxylase is possible late in the 1st trimester by analysis of DNA obtained by chorionic villus sampling or during the 2nd trimester by amniocentesis. This is usually done because the parents already have an affected child. Most often, the CYP21 gene is analyzed for frequently occurring mutations; more rare mutations may be detected by DNA sequencing.

NEWBORN SCREENING
Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency, all states in the United States and many other countries have instituted newborn screening programs. These programs analyze 17-hydroxyprogesterone levels in dried blood obtained by heelstick and absorbed on filter paper cards; the same cards are screened in parallel for other congenital conditions, such as hypothyroidism and phenylketonuria. Potentially affected infants are typically quickly recalled for additional testing (electrolytes and repeat 17-hydroxyprogesterone determination) at approximately 2 wk of age. Infants with salt-wasting disease often have abnormal electrolytes by this age but are usually not severely ill. Thus, screening programs are effective in preventing many cases of adrenal crisis in affected males. The nonclassic form of the disease is not reliably detected by newborn screening, but this is of little clinical significance because adrenal insufficiency does not occur in this type of 21-hydroxylase deficiency.

The main difficulty with current newborn screening programs is that to reliably detect all affected infants, the cutoff 17-hydroxyprogesterone levels for recalls are set so low that there is a very high frequency of false-positive results (i.e., the test has a low positive predictive value
of approximately 1%). This problem is worst in premature infants. Positive predictive value can be improved by using cutoff levels based on gestational age, and by utilizing more specific second-tier screening methods such as liquid chromatography followed by tandem mass spectrometry.

**TREATMENT**

**Glucocorticoid Replacement**

Cortisol deficiency is treated with glucocorticoids. Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization. This often requires larger glucocorticoid doses than are needed in other forms of adrenal insufficiency, typically 15-20 mg/m2/24 hr of hydrocortisone daily administered orally in 3 divided doses. Infants usually require dosing at the high end of this range. Double or triple doses are indicated during periods of stress, such as infection or surgery. Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present. Therapy must be individualized. It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles often indicates overtreatment with glucocorticoids. Overtreatment is also suggested by excessive weight gain. Pubertal development should be monitored by periodic examination, and sexual maturation is evaluated by serial radiographs of the hand and wrist for bone age. Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning, before taking the morning medications, or at a consistent time in relation to medication dosing. In general, desirable 17-hydroxyprogesterone levels are in the high-normal range or several times normal; low-normal levels can usually be achieved only with excessive glucocorticoid doses.

Menarche occurs at the appropriate age in most girls in whom good control has been achieved; it may be delayed in girls with suboptimal control. Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3-7 yr of age, at which time skeletal maturation may be 5 yr or more in advance of chronological age. In some children, especially if the bone age is 12 yr or more, spontaneous central (i.e., gonadotropin-dependent) puberty may occur when treatment is instituted, because therapy with hydrocortisone suppresses production of adrenal androgens and thus stimulates release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. This form of superimposed true precocious puberty may be treated with a gonadotropin hormone–releasing hormone analog such as leuprolide (see Chapter 562). Males with 21-hydroxylase deficiency who have had inadequate corticosteroid therapy may develop testicular adrenal rest tumors, which usually regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow Doppler examination help define the character and extent of disease. Testis-sparing surgery for steroid-unresponsive tumors has been reported.

**Mineralocorticoid Replacement**

Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone. Infants may have very high mineralocorticoid requirements in the first few months of life, usually 0.1-0.3 mg daily in 2 divided doses but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride, 8 mmol/kg) in addition to the mineralocorticoid. Older infants and children are usually maintained with 0.05-0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even when these patients have normal aldosterone levels in the absence of mineralocorticoid replacement. Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids. Serum electrolytes should be measured frequently in early infancy as therapy is adjusted. Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.

Additional approaches to improve outcome have been proposed but have not yet become the standard of care. These include an antiandrogen such as flutamide to block the effects of excessive androgen levels, and/or an aromatase inhibitor such as anastrozole, which blocks conversion of androgens to estrogen and thus retards skeletal maturation, a process that is sensitive to estrogens in both boys and girls. Aromatase inhibitors generally should not be used in pubertal girls because they will obviously retard normal puberty and may expose the ovaries to excessive levels of gonadotropins. Growth hormone, with or without luteinizing hormone–releasing hormone agonists to retard skeletal maturation, has been suggested to improve adult height.

**Surgical Management of Ambiguous Genitals**

Significantly virilized females usually undergo surgery between 2-6 mo of age. If there is severe clitoromegaly, the clitoris is reduced in size, with partial excision of the corporal bodies and preservation of the neurovascular bundle; however, moderate clitoromegaly may become much less noticeable even without surgery as the patient grows. Vaginoplasty and correction of the urogenital sinus usually are performed at the time of clitoral surgery; revision in adolescence is often necessary.

Risks and benefits of surgery should be fully discussed with parents of affected females. There is limited long-term follow-up of functional outcomes in patients who have undergone modern surgical procedures. It appears that female sexual dysfunction increases in frequency and severity in those with the most significant degrees of genital virilization and with the degree of enzymatic impairment (prenatal androgen exposure) caused by each patient’s mutations (see Table 576-2). Sex assignment of infants with disorders of sexual differentiation (including CAH) is usually based on expected sexual functioning and fertility in adulthood with early surgical correction of the external genitals to conform with the sex assignment. Confused gender identity is not common with CAH; it occurs mostly in females with the salt-wasting form of the disease and the greatest degree of virilization.

Lay and medical opponents of genital surgery for other disorders of sexual differentiation state that it ignores any prenatally biased gender role predisposition from androgen exposure and precludes the patient from having any decision as to the patient’s own preferred sexual identity and what surgical correction of the genitals should be performed. These individuals and groups say treatment should be aimed primarily at educating the patient, family, and others about the medical condition, its treatment, and how to deal with the intersex condition. They propose that surgery should be delayed until the patient decides on what, if any, correction should be performed. Severely virilized genotypic (XX) females raised as males have generally functioned well in the male gender as adults.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency (hirsutism, obesity, amenorrhea), bilateral laparoscopic adrenalectomy (with hormone replacement) may be an alternative to standard medical hormone replacement therapy, but patients treated in this way may be more susceptible to acute adrenal insufficiency if treatment is interrupted because the adrenal glands have been removed. Moreover, they may exhibit signs of elevated ACTH levels such as abnormal pigmentation.

**Prenatal Treatment**

Besides genetic counseling, the main goal of prenatal treatment is to facilitate appropriate prenatal treatment of affected females. Mothers with pregnancies at risk are given dexamethasone, a steroid that readily crosses the placenta, in an amount of 20 μg/kg prepregnancy maternal weight daily in 2 or 3 divided doses. This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. If started by 6 wk of gestation, it ameliorates virilization of the external
genitalia in affected females. Chorionic villus biopsy is then performed to determine the sex and genotype of the fetus; therapy is continued only if the fetus is an affected female. DNA analysis of fetal cells isolated from maternal plasma for sex determination and CYP21 gene analysis may permit earlier identification of the affected female fetus. Children exposed to this therapy may have slightly lower birthweights. Effects on personality or cognition, such as increased shyness, have been suggested but not consistently observed. At present there is insufficient information to determine whether the long-term risks are acceptable, particularly in the males and unaffected females who derive no direct benefit from the treatment. Maternal side effects of prenatal treatment have included edema, excessive weight gain, hypertension, glucose intolerance, cushingoid facial features, and severe striae. Prenatal treatment is therefore carried out only under institutional protocols in some locales, but it is offered as an option outside the research setting by high-risk obstetricians in other communities.

Bibliography is available at Expert Consult.

576.2 Congenital Adrenal Hyperplasia Caused by 11β-Hydroxylase Deficiency

Perrin C. White

ETIOLOGY

Deficiency of 11β-hydroxylase is caused by a mutation in the CYP11B1 gene located on chromosome 8q24. CYP11B1 mediates 11-hydroxylation of 11-deoxycorticisol to cortisol. Because 11-deoxycorticisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors—particularly 11-deoxycorticisol and deoxycorticocorterone—accumulate and are shunted into androgen biosynthesis in the same manner as occurs in 21-hydroxylase deficiency. The adjacent CYP11B2 gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally.

EPIDEMIOLOGY

11β-Hydroxylase deficiency accounts for approximately 5% of cases of adrenal hyperplasia; its incidence in the general population has been estimated as 1 in 250,000 to 1 in 100,000. The disorder occurs relatively frequently in Israeli Jews of North African origin (1 in 15,000-17,000 live births). In this ethnic group almost all alleles carry an Arg448 to His (R448H) mutation in CYP11B1, but many other mutations have been identified. This disorder presents in a classic, severe form and very rarely in a nonclassic, milder form.

CLINICAL MANIFESTATIONS

Although cortisol is not synthesized efficiently, aldosterone synthetic capacity is normal, and some corticosterone is synthesized from progesterone by the intact aldosterone synthase enzyme. Thus, it is unusual for patients to manifest signs of adrenal insufficiency such as hypotension, hypoglycemia, hyponatremia, and hyperkalemia. Approximately 65% of patients become hypertensive, although this can take several years to develop. Hypertension is probably a consequence of elevated levels of deoxycorticosterone, which has mineralocorticoid activity. Infants may transiently develop signs of mineralocorticoid deficiency after treatment with hydrocortisone is instituted. This is presumably from sudden suppression of deoxycorticosterone secretion in a patient with atrophy of the zona glomerulosa caused by chronic suppression of renin activity.

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency may also occur in 11β-hydroxylase deficiency.

LABORATORY FINDINGS

Plasma levels of 11-deoxycorticisol and deoxycorticosterone are elevated. Because deoxycorticosterone and metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low even though the ability to synthesize aldosterone is intact. Hypokalemic alkalosis occasionally occurs.

TREATMENT

Patients are treated with hydrocortisone in doses similar to those used for 21-hydroxylase deficiency. Mineralocorticoid replacement is sometimes transiently required in infancy but is rarely necessary otherwise. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it is of long standing. Calcium channel blockers may be beneficial under these circumstances.

Bibliography is available at Expert Consult.

576.3 Congenital Adrenal Hyperplasia Caused by 3β-Hydroxysteroid Dehydrogenase Deficiency

Perrin C. White

ETIOLOGY

Deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) occurs in fewer than 2% of patients with adrenal hyperplasia. This enzyme is required for conversion of Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, dehydroepiandrosterone [DHEA]) to Δ4 steroids (progesterone, 17-hydroxyprogesterone, and androstenedione). Thus, deficiency of the enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA (see Fig. 574-1 in Chapter 574). The 3β-HSD isozyme expressed in the adrenal cortex and gonad is encoded by the HSD3B2 gene located on chromosome 1p13.1. Over 30 mutations in the HSD3B2 gene have been described in patients with 3β-HSD deficiency.

CLINICAL MANIFESTATIONS

Because cortisol and aldosterone are not synthesized in patients with the classic form of the disease, infants are prone to salt-wasting crises. Because androstenedione and testosterone are not synthesized, boys are incompletely virilized. Varying degrees of hypospadia may occur, with or without bifid scrotum or cryptorchidism. Because DHEA levels are elevated and this hormone is a weak androgen, girls may be mildly virilized, with slight to moderate clitoral enlargement. Postnatally, continued excessive DHEA secretion can cause precocious adrenarche. During adolescence and adulthood, hirsutism, irregular menses, and polycystic ovarian disease occur in females. Males manifest variable degrees of hypogonadism, although appropriate male secondary sexual development may occur. A persistent defect of testicular 3β-HSD is demonstrated, however, by the high Δ5:Δ4 steroid ratio in testicular effluent.

LABORATORY FINDINGS

The hallmark of this disorder is the marked elevation of the Δ5 steroids (such as 17-hydroxypregnenolone and DHEA) preceding the enzymatic block. Patients may also have elevated levels of 17-hydroxyprogesterone because of the extraadrenal 3β-HSD activity that occurs in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency. The ratio of 17-hydroxypregnenolone:17-hydroxyprogesterone is markedly elevated in 3β-HSD deficiency, in contrast to the decreased ratio in 21-hydroxylase deficiency. Plasma renin activity is elevated in the salt-wasting form.

DIFFERENTIAL DIAGNOSIS

It is not unusual for children with premature adrenarche, or women with signs of androgen excess, to have mild to moderate elevations in DHEA levels. It has been suggested that such individuals have “nonclassic 3β-HSD deficiency.” Mutations in the HSD3B2 gene are usually not found in such individuals, and a nonclassic form of this deficiency must actually be quite rare. The activity of 3β-HSD in the adrenal zonae
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fasciculata and reticularis, relative to CYP17 (17-hydroxylase/17,20-lyase) activity, normally decreases during adrenarche to facilitate DHEA synthesis, and so modest elevations in DHEA in preteenage children or women usually represent a normal variant.

**TREATMENT**

Patients require glucocorticoid and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency. Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of 25 mg every 4 wk of a depot form of testosterone early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

*Bibliography is available at Expert Consult.*

### 576.4 Congenital Adrenal Hyperplasia Caused by 17-Hydroxylase Deficiency

**Perrin C. White**

**ETIOLOGY**

Less than 1% of CAH cases are caused by 17-hydroxylase deficiency, but the condition is apparently more common in Brazil and China. A single polypeptide, CYP17, catalyzes 2 distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxyprogrenolone and 17-hydroxyprogesterone, respectively, and the 17,20-lyase reaction mediating conversion of 17-hydroxyprogrenolone to DHEA and, to a lesser extent, 17-hydroxyprogesterone to A4-androstenedione. DHEA and androstenedione are steroid precursors of testosterone and estrogen (see Fig. 574-1 in Chapter 574). The enzyme is expressed in both the adrenal cortex and the gonads and is encoded by a gene on chromosome 10q24.3. Most mutations affect both the hydroxylase and lyase activities, but rare mutations can affect either activity alone.

Mutations in genes other than CYP17 can have the same phenotype as 17,20-lyase deficiency (i.e., deficient androgen synthesis with normal cortisol synthesis). These include an accessory electron transfer protein, cytochrome b5, and mutations in 2 aldo-keto reductases, AKR1C2 and AKR1C4. These AKR1C isozymes normally catalyze 3α-hydroxysteroid dehydrogenase activity, which allows synthesis of the potent androgen dihydrotestosterone through an alternative “backdoor” biosynthetic pathway that does not include testosterone as an intermediate.

**CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS**

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause hypertension, hypokalemia, and suppression of renin and aldosterone secretion, as occurs in 11β-hydroxylase deficiency. In contrast to 11β-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. Affected **males are incompletely virilized** and present as phenotypic females (but gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with **failure of sexual development** at the expected time of puberty. 17-Hydroxylase deficiency in females must be considered in the differential diagnosis of primary hypogonadism (see Chapter 586). Levels of deoxycorticosterone are elevated and renin and aldosterone are consequently suppressed. Cortisol and sex steroids are unresponsive to stimulation with ACTH and human chorionic gonadotropin, respectively.

Patients with isolated 17,20-lyase deficiency have deficient androgen synthesis with normal cortisol synthesis, and therefore do not become hypertensive.

**TREATMENT**

Patients with 17-hydroxylase deficiency require cortisol replacement to suppress secretion of deoxycorticosterone and thus control hypertension. Additional antihypertensive medication may be required. Females require estrogen replacement at puberty. Genetic males may require either estrogen or androgen supplementation depending on the sex of rearing. Because of the possibility of malignant transformation of abdominal testes with androgen insensitivity syndrome (see Chapter 588.2), genetic males with severe 17-hydroxylase deficiency being reared as females require gonadectomy at or before adolescence.

*Bibliography is available at Expert Consult.*

### 576.5 Lipoid Adrenal Hyperplasia

**Perrin C. White**

**ETIOLOGY**

Lipoid adrenal hyperplasia is a rare disorder, most frequently found in Japanese persons. Patients with this disorder exhibit marked accumulation of cholesterol and lipids in the adrenal cortex and gonads, associated with severe impairment of all steroidogenesis. Lipoid adrenal hyperplasia is usually caused by mutations in the gene for steroidogenic acute regulatory protein (StAR), a mitochondrial protein that promotes the movement of cholesterol from the outer to the inner mitochondrial membrane. However, mutations in the CYP11A1 gene (which encodes the cholesterol side chain cleavage enzyme) have been reported in several patients.

Some cholesterol is able to enter mitochondria even in the absence of StAR, so it might be supposed that this disorder would not completely impair steroid biosynthesis. However, the accumulation of cholesterol in the cytoplasm is cytotoxic, eventually leading to death of all steroidogenic cells in which StAR is normally expressed. This occurs prenatally in the adrenals and testes. The ovaries do not normally synthesize steroids until puberty, so cholesterol does not accumulate and the ovaries can retain the capacity to synthesize estrogens until adolescence.

Although estrogens synthesized by the placenta are required to maintain pregnancy, the placenta does not require StAR for steroid biosynthesis. Thus, mutations of StAR are not prenatally lethal.

**CLINICAL MANIFESTATIONS**

Patients with lipoid adrenal hyperplasia are usually unable to synthesize any adrenal steroids. Thus, affected infants are likely to be confused with those with adrenal hypoplasia congenita. Salt-losing manifestations are typical, and many infants die in early infancy. Genetic males are unable to synthesize androgens and thus are **phenotypically female** but with gonads palpable in the labia majora or inguinal areas. Genetic females appear normal at birth and may undergo feminization at puberty with menstrual bleeding. They too, progress to hypergonadotropic hypogonadism when accumulated cholesterol kills granulosa (i.e., steroid synthesizing) cells in the ovary.

**LABORATORY FINDINGS**

Adrenal and gonadal steroid hormone levels are low in lipid adrenal hyperplasia, with a decreased or absent response to stimulation (ACTH, human chorionic gonadotropin). Plasma renin levels are increased.

Imaging studies of the adrenal gland demonstrating massive adrenal enlargement in the newborn help establish the diagnosis of lipid adrenal hyperplasia.

**TREATMENT**

Patients require glucocorticoid and mineralocorticoid replacement. Genetic males are usually assigned a female sex of rearing; thus both genetic males and females require estrogen replacement at the expected age of puberty.

*Bibliography is available at Expert Consult.*
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576.6 Deficiency of P450 Oxidoreductase (Antley-Bixler Syndrome)  

**ETIOLOGY, PATHOGENESIS, AND CLINICAL MANIFESTATIONS**

P450 oxidoreductase (POR, gene located on chromosome 7q11.3) is required for the activity of all microsomal cytochrome P450 enzymes (see Chapter 574) including the adrenal enzymes CYP17 and CYP21. Thus, complete POR deficiency abolishes all microsomal P450 activity. This is embryonically lethal in mice and presumably in humans as well. Patients with mutations that decrease but do not abolish POR activity have partial deficiencies of 17-hydroxylase and 21-hydroxylase activities in the adrenals. A single recurrent mutation, A287P (alanine-287 to proline) is found on approximately 40% of alleles.

Deficiency of 17-hydroxylase leads to incomplete masculinization in males; 21-hydroxylase deficiency may lead to virilization in females. Additionally, aromatase (CYP19) activity in the placenta is decreased, leading to unopposed action of androgens produced by the fetal adrenal. This exacerbates virilization of female fetuses and may virilize the mother of an affected fetus as well. Although it is puzzling that affected females could be virilized despite a partial deficiency in CYP17 (which is required for androgen biosynthesis), an alternative (“back-door”) biosynthetic pathway is utilized in which 17-hydroxyprogesterone is converted to 5α-pregnane-3α,17α-diol-20-one, a metabolite that is a much better substrate for the 17,20-lyase activity of CYP17 than the usual substrate, 17-hydroxyprogrenolonol (see Chapter 574). The metabolite is then converted in several enzymatic steps to dihydrotestosterone, a potent androgen.

Because many other P450 enzymes are affected, patients often (but not invariably) have other congenital anomalies collectively referred to as Antley-Bixler syndrome. These include craniosynostosis; brachycephaly; frontal bossing; severe midface hypoplasia with proptosis and choanal stenosis or atresia; humeroradial synostosis; medial bowing of ulnas; long, slender fingers with camptodactyly; narrow iliac wings; anterior bowing of femurs; and malformations of the heart and kidneys. Studies of mutant mice suggest that the metabolic defects responsible for these anomalies include defective metabolism of retinoic acid, leading to elevated levels of this teratogenic compound, and deficient biosynthesis of cholesterol.

**EPIDEMIOLOGY**

The prevalence is not known with certainty. It must be rare compared with 21-hydroxylase deficiency but might occur at similar frequencies to the other forms of CAH.

**LABORATORY FINDINGS**

Serum steroids that are not 17- or 21-hydroxylated are most increased, including pregnenolone and progesterone. 17-Hydroxy, 21-deoxysteroids are also increased, including 17-hydroxyprogrenolone, 17-hydroxyprogesterone, and 21-deoxycortisol. Urinary steroid metabolites may be determined by quantitative mass spectrometry. Metabolites excreted at increased levels include pregnanediol, pregnanetriol, pregnanetrionelone, and corticosterone metabolites. Urinary cortisol metabolites are decreased. Genetic analysis demonstrates mutations in the POR gene.

**DIFFERENTIAL DIAGNOSIS**

This disorder must be distinguished from other forms of CAH, particularly 21-hydroxylase deficiency in females, which is far more common and has similar laboratory findings. Suspicin for POR deficiency may be raised if the mother is virilized or if the associated abnormalities of Antley-Bixler syndrome are present. Conversely, virilization of both the mother and her daughter can result from a luteoma of pregnancy, but in this case postnatal abnormalities of corticosteroid biosynthesis should not be observed. Antley-Bixler syndrome may also occur without abnormalities of steroid hormone biosynthesis, resulting from mutations in the fibroblast growth factor receptor FGFR2.

Bibliography is available at Expert Consult.

576.7 Aldosterone Synthase Deficiency  

**ETIOLOGY**

This is a rare autosomal recessive disorder in which conversion of corticosterone to aldosterone is impaired; a group of Iranian Jewish patients has been the most thoroughly studied. The majority of cases result from mutations in the CYP11B2 gene coding for aldosterone synthase; however, linkage to CYP11B2 has been excluded in other kindreds. When not caused by CYP11B2 mutations, the disorder has been termed familial hyperreninemic hypoaldosteronism type 2; the causative gene or genes have not yet been identified.

Aldosterone synthase mediates the 3 final steps in the synthesis of aldosterone from deoxycorticosterone (11β-hydroxylation, 18-hydroxylation, and 18-oxidation). Although 11β-hydroxylation is required to convert deoxycorticosterone to corticosterone, this conversion can also be catalyzed by the related enzyme, CYP11B1, located in the fasciculata, which is unaffected in this disorder. For the same reason, these patients have normal cortisol biosynthesis.

The disease has been classified into 2 types, termed aldosterone methylxidase deficiency types I and II. They differ only in levels of the immediate precursor of aldosterone, 18-hydroxycorticosterone; levels are low in type I deficiency and elevated in type II deficiency. These differences do not correspond in a simple way to particular mutations and are of limited clinical importance.

**CLINICAL MANIFESTATIONS**

Infants with aldosterone synthase deficiency may have severe electrolyte abnormalities with hyponatremia, hyperkalemia, and metabolic acidosis. Because cortisol synthesis is unaffected, infants rarely become as ill as untreated infants with salt-losing forms of CAH such as 21-hydroxylase deficiency. Thus, some infants escape diagnosis. Later in infancy or in early childhood they may exhibit failure to thrive and poor growth. Adults often are asymptomatic, although they may develop electrolyte abnormalities when depleted of sodium through procedures such as bowel preparation for a barium enema.

**LABORATORY FINDINGS**

Infants have elevated plasma renin activity. Aldosterone levels are decreased; they may be at the lower end of the normal range but are always inappropiately low for the degree of hyperkalemia or hyperreninemia. Corticosterone levels are often elevated.

Some, but not all, patients have marked elevation of 18-hydroxycorticosterone; however, low levels of this steroid do not exclude the diagnosis. In those kindreds in which 18-hydroxycorticosterone levels are elevated in affected individuals, this biochemical abnormality persists in adults even when they have no electrolyte abnormalities.

**DIFFERENTIAL DIAGNOSIS**

It is important to distinguish aldosterone synthase deficiency from primary adrenal insufficiency in which both cortisol and aldosterone are affected (including salt-wasting forms of CAH) because the latter condition is usually associated with a much greater risk of shock and hyponatremia. This becomes apparent after the appropriate laboratory studies. Adrenal hypoplasia congenita may initially present with aldosterone deficiency; all male infants with apparently isolated aldosterone deficiency should be carefully monitored for subsequent development of cortisol deficiency. Pseudohypoaldosteronism (see Chapter 575.4) may have similar electrolyte abnormalities and
Bibliography


TREATMENT
Glucocorticoid-suppressible hyperaldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone, 25 µg/kg/day in divided doses. If necessary, effects of aldosterone can be blocked with a potassium-sparing diuretic such as spironolactone, eplerenone, or amiloride. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If hypertension is long standing, additional antihypertensive medication may be required, such as a calcium channel blocker.

GENETIC COUNSELING
Because of the autosomal dominant mode of inheritance, at-risk family members should be investigated for this easily treated cause of hypertension.

576.8 Glucocorticoid-Suppressible Hyperaldosteronism
Perrin C. White

ETIOLOGY
Glucocorticoid-suppressible hyperaldosteronism (glucocorticoid-remediable aldosteronism, familial hyperaldosteronism type I) is an autosomal dominant form of low-renin hypertension in which hyperaldosteronism is rapidly suppressed by glucocorticoid administration. This unusual effect of glucocorticoids suggests that aldosterone secretion in this disorder is regulated by ACTH instead of by the renin-angiotensin system. In addition to abnormally regulated secretion of aldosterone, there is marked overproduction of 18-hydroxycortisol and 18-oxocortisol. The synthesis of these steroids requires both 17-hydroxylase (CYP17) activity, which is expressed only in the zona fasciculata, and aldosterone synthase (CYP11B2) activity, which is normally expressed only in the zona glomerulosa. Together, these features imply that aldosterone synthase is being expressed in a manner similar to the closely related enzyme steroid 11-hydroxylase (CYP11B1). The disorder is caused by unequal meiotic crossing-over events between the CYP11B1 and CYP11B2 genes, which are closely linked on chromosome 8q24. An additional "hybrid" gene is produced, having regulatory sequences of CYP11B1 juxtaposed with coding sequences of CYP11B2. This results in the inappropriate expression of a CYP11B2-like enzyme with aldosterone synthase activity in the adrenal fasciculata.

CLINICAL MANIFESTATIONS
Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension, typically approximately 30 mm Hg higher than unaffected family members of the same age. Others have more symptomatic hypertension with headache, dizziness, and visual disturbances. A strong family history of early-onset hypertension or early strokes may alert the clinician to the diagnosis. Some patients have chronic hypokalemia, but this is not a consistent finding and is usually mild.

LABORATORY FINDINGS
Patients have elevated plasma and urine levels of aldosterone and suppressed plasma renin activity. Hypokalemia is not consistently present. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol are markedly increased. The hybrid CYP11B1/CYP11B2 gene can be readily detected by molecular genetic methods.

DIFFERENTIAL DIAGNOSIS
This condition should be distinguished from primary aldosteronism based on bilateral hyperplasia or an aldosterone-producing adenoma (see Chapter 578). Most cases of primary aldosteronism are sporadic, although several affected kindreds have been reported. Patients with primary aldosteronism may also have elevated levels of 18-hydroxycortisol and 18-oxocortisol, and these biochemical tests should be used cautiously to distinguish primary and glucocorticoid-suppressible aldosteronism. A therapeutic trial of dexamethasone may be helpful if aldosterone secretion is suppressed, and genetic testing should identify the hybrid gene of glucocorticoid-suppressible hyperaldosteronism if it is present.
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Chapter 577

Cushing Syndrome

Perrin C. White

Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, a result of either an adrenal tumor or of hypersecretion of corticotropin (adrenocorticotropic hormone [ACTH]) by the pituitary (Cushing disease) or by a tumor (Table 577-1).

**ETIOLOGY**

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. This rarely represents a diagnostic challenge, but management of hyperglycemia, hypertension, weight gain, linear growth retardation, and osteoporosis often complicates therapy with corticosteroids.

**Endogenous Cushing syndrome** is most often caused in infants by a functioning adrenocortical tumor (see Chapter 579). Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing syndrome in children older than 7 yr of age is **Cushing disease**, in which excessive ACTH secreted by a pituitary adenoma causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed microadenomas. They consist principally of chromophobe cells and frequently show positive immunostaining for ACTH and its precursor, proopiomelanocortin. Whereas the vast majority of such tumors are sporadic, a small number occur in kindreds with familial isolated pituitary adenoma syndrome. This syndrome, which is caused by mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene, accounts for perhaps 2% of pituitary adenomas, but more commonly tumors with AIP mutations secrete growth hormone or prolactin, and only rarely do they secrete ACTH. Similarly, multiple endocrine neoplasia type 1 (MEN1) patients, who by definition have mutations in the MEN1 (menin) gene, may develop pituitary tumors, but these are typically prolactinomas.

ACTH-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic
ACTH secretion in children is associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangio-pericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more common in the ectopic ACTH syndrome than in other forms of Cushing syndrome, because very high cortisol levels may overwhelm 11β-hydroxysteroid dehydrogenase in the kidney (see Chapter 575) and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas (which are discussed in Chapter 579). Primary pigmented nodular adrenocortical disease (PPNAD) is a distinctive form of ACTH-independent Cushing syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands are small and have characteristic multiple, small (<4 mm in diameter), pigmented (black) nodules containing large cells with cytoplasm and lipofuscin; there is corticol atrophy between the nodules. This adrenal disorder occurs as a component of Carney complex, an autosomal dominant disorder also consisting of centrofacial lentigines and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A (PRKAR1A) on chromosome 17q22-24 and less frequently to chromosome 2p16. Patients with Carney complex and PRKAR1A mutations generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. Conversely, children presenting with PPNAD as an isolated finding rarely have mutations in PRKAR1A, or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have mutations in the PDE8B or PDE11A genes encoding different phosphodiesterase isozymes.

ACTH-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of McCune-Albright syndrome, with symptoms beginning in infancy or childhood. McCune-Albright syndrome is caused by a somatic mutation of the GNAS gene encoding the G protein, Gα, through which the ACTH receptor (MC2R) normally signals. This results in inhibition of guanine triphosphatase activity and constitutive activation of adenylyl cyclase, thus increasing levels of cyclic adenosine monophosphate. When the mutation is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

Thus the genes causing nodular adrenocortical hyperplasia that have been identified thus far all produce overactivity of the ACTH signaling pathway either by constitutively activating Gα (McCune-Albright syndrome), by reducing the breakdown of cyclic adenosine monophosphate and thus increasing its intracellular levels (mutations of PDE8B or PDE11A), or by disrupting the regulation of the cyclic adenosine monophosphate–dependent enzyme, protein kinase A (PRKAR1A mutations).

Additionally, adrenocortical lesions including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma may occur as part of the MEN1 syndrome (see Chapter 573), an autosomal dominant disorder, in which there is homozygous inactivation of the menin (MEN1) tumor-suppressor gene on chromosome 11q13.

### Clinical Manifestations

Signs of Cushing syndrome have been recognized in infants younger than 1 yr of age. The disorder appears to be more severe and the clinical findings more flagrant in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in girls. Growth is impaired, with length falling below the 3rd percentile, except when significant virilization produces normal or even accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

In older children, in addition to obesity, short stature is a common presenting feature. Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. Purplish striae on the hips, abdomen, and thighs are common. Pubertal development may be delayed, or amenorrhea may occur in girls past menarche. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis is common and may cause pathologic fractures.

### Laboratory Findings

Cortisol levels in blood are normally highest at 8 AM and decrease to less than 50% by midnight except in infants and young children in whom a diurnal rhythm is not always established. In patients with Cushing syndrome this circadian rhythm is lost; midnight cortisol levels >4.4 μg/dL strongly suggest the diagnosis. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in saliva samples, which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing syndrome.

Urinary excretion of free cortisol is increased. This is best measured in a 24 hr urine sample and is expressed as a ratio of micrograms of cortisol excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.
A single-dose dexamethasone suppression test is often helpful; a dose of 25-30 µg/kg (maximum: 2 mg) given at 11 PM results in a plasma cortisol level of less than 5 µg/dL at 8 AM the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure adequacy of dosing.

A glucose tolerance test is often abnormal but is of no diagnostic utility. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor. ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors and are very high in patients with ectopic ACTH-secreting tumors but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone, patients with ACTH-dependent Cushing syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The 2-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120 µg/kg/24 hr in 4 divided doses, on consecutive days. In children with pituitary/Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing syndrome do not show suppressed cortisol levels with dexamethasone.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after corticotropin-releasing hormone administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers, and moreover may be of decreased specificity in children.

DIFFERENTIAL DIAGNOSIS
Cushing syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are usually normal and cortisol secretion is suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing syndrome occur in patients with generalized glucocorticoid resistance (see Chapter 575.4). Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

TREATMENT
Transsphenoidal pituitary microsurgery is the treatment of choice in pituitary Cushing disease in children. The overall success rate with follow-up of less than 10 yr is 60-80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in the majority of cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing disease in adults; remissions are usually not sustained after discontinuation of therapy. This agent is rarely used in children. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. Mifepristone, a glucocorticoid receptor antagonist, has been used in a limited number of cases.
Bibliography


Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the renin–angiotensin system. These disorders are characterized by **hypertension**, **hypokalemia**, and suppression of the renin–angiotensin system.

**ETIOLOGY**
Aldosterone-secreting adenomas are unilateral and have been reported in children as young as 3.5 yr of age; they mainly affect girls. Adrenocortical tumors are discussed further in Chapter 579. Bilateral micronodular adrenocortical hyperplasia tends to occur in older children and is more frequent in males. Primary aldosteronism due to unilateral adrenal hyperplasia may also occur. Glucocorticoid-suppressible hyperaldosteronism is discussed in Chapter 576.8.

**EPIDEMIOLOGY**
These conditions are thought to be rare in children, but they may account for 5-10% of cases of hypertension in adults. Although usually sporadic, kindreds with several affected members have been reported. Genetic linkage to chromosome 7p22 has been identified in some of these kindreds, but the involved gene has not yet been identified. Mutations in the *KCNJ5* gene on chromosome 11q24 have been identified in several kindreds; these mutations (G151R and G151E) altered channel selectivity, producing increased Na⁺ conductance and membrane depolarization, which increases aldosterone production and proliferation of adrenal glomerulosa cells. Moreover, such mutations have been identified in a subset of sporadic aldosterone-producing adenomas.
CLINICAL MANIFESTATIONS
Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others have severe hypertension (up to 240/150 mm Hg), with headache, dizziness, and visual disturbances. Chronic hypokalemia, if present, may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, tetany, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

LABORATORY FINDINGS
Hypokalemia occurs frequently. Serum pH and the carbon dioxide and sodium concentrations may be elevated and the serum chloride and magnesium levels decreased. Serum levels of calcium are normal, even in children who manifest tetany. The urine is neutral or alkaline, and urinary potassium excretion is high. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24 hr urine collections are always increased. Plasma levels of renin are persistently low.

The diagnostic test of choice for primary aldosteronism is controversial. Both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. It is desirable to establish a consistent sampling protocol, for example, at midmorning after the patient has been sitting for 15 min. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks prior to testing, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal antiinflammatory agents. Patients taking these agents may need to be changed to α-adrenergic blockers or calcium channel blockers that have smaller effects on the biochemical measurements. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism. Aldosterone does not decrease with administration of saline solution or fludrocortisone, and renin does not respond to salt and fluid restriction. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol may be increased but not to the extent seen in glucocorticoid-suppressible hyperaldosteronism.

DIFFERENTIAL DIAGNOSIS
Primary aldosteronism should be distinguished from glucocorticoid-suppressible hyperaldosteronism (see Chapter 576.8), which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. Glucocorticoid-suppressible hyperaldosteronism is diagnosed by dexamethasone suppression tests or by specific genetic testing. More generally, primary aldosteronism should be distinguished from other forms of hypertension by means of the testing previously discussed.

TREATMENT
The treatment of an aldosterone-producing adenoma is surgical removal. This is performed primarily by laparotomy and adrenalectomy; successful enucleation of aldosterone-producing adenomas, as well as laparoscopic adrenalectomy, has been reported. Hyperaldosteronism caused by bilateral adrenal hyperplasia is treated with the mineralocorticoid antagonists spironolactone (1-3 mg/kg/day to a maximum of 100 mg/day) or eplerenone (25-100 mg/day in 2 divided doses), often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandro- genic properties that may be unacceptable in pubertal males. Eplerenone is a more specific antimineralocorticoid that is safe in children, but there is little specific experience with primary aldosteronism in the pediatric age group. As an alternative, an epithelial sodium channel blocker, such as amiloride, may be used, with other antihypertensive agents added as necessary. In patients whose condition cannot be controlled medically, unilateral adrenalectomy may be considered.

Bibliography is available at Expert Consult.
Bibliography


Adrenocortical Tumors
Perrin C. White

**EPIDEMIOLOGY**
Adrenocortical tumors are rare in childhood, with an incidence of 0.3-0.5 cases per 1 million child-years. They occur in all age groups but most commonly in children younger than 6 yr of age, and are more frequent (1.6-fold) in girls. In 2-10% of cases, the tumors are bilateral. Almost half of childhood adrenocortical tumors are carcinomas.

Symptoms of endocrine hyperfunction are present in 80-90% of children with adrenal tumors (see Table 577-1 in Chapter 577). Tumors that secrete cortisol and aldosterone are also discussed in Chapters 577 and 578, respectively. Tumors may be associated with hemihypertrophy, usually occurring during the 1st few yr of life. They are also associated with other congenital defects, particularly genitourinary tract and central nervous system abnormalities and hamartomatous defects.

**ETIOLOGY**
The incidence of adrenocortical tumors is increased in several familial cancer syndromes resulting from abnormalities in genes that encode transcription factors implicated in cell proliferation, differentiation, senescence, apoptosis, and genomic instability. These include tumor protein 53 (TP53), menin (the **MEN1** gene involved in multiple endocrine neoplasia type 1), the **APC** gene involved in familial adenomatous polyposis coli, and the **PRKAR1A** gene encoding a cyclic adenosine monophosphate–dependent protein kinase regulatory subunit (also see Chapter 577).

Germline mutations in **TP53** (on chromosome 17p13.1) have been found in patients with isolated adrenal carcinoma as well as in patients with familial clustering of unusual malignancies; this latter condition is termed **Li-Fraumeni syndrome**. A 15-fold increased incidence of childhood adrenocortical tumors is found in southern Brazil, associated with a R337H mutation in **TP53**. Overexpression of insulin-like growth factor 2 (encoded by **IGF2**, on chromosome 11p15.5) occurs in 80% of sporadic childhood adrenocortical tumors, as well as in those associated with **Beckwith-Wiedemann syndrome**, in which there is loss of the normal imprinting of genes in this chromosomal region. Further implicating insulin-like growth factors (IGFs) in pathogenesis, many pediatric adrenocortical tumors overexpress the IGF receptor, IGF1R. Overexpression of steroidogenic factor-1 (SF1), a transcription factor required for adrenal development (see Chapter 574) is associated with decreased overall survival and recurrence-free survival when it occurs in adults with adrenocortical carcinomas, but it is seen in most pediatric adrenocortical tumors, where it does not seem to have prognostic significance. Conversely, the messenger RNA encoding the nephroblastoma overexpressed (NOV) protein (also termed cysteine-rich protein 61, or connective tissue growth factor, or nephroblastoma overexpressed gene-3) is significantly downregulated in childhood adrenocortical tumors. NOV is a selective pro-apoptotic factor for human adrenocortical cells, suggesting that abnormal apoptosis may play a role in childhood adrenocortical tumorigenesis.

Aldosterone-producing adenomas constitute a separate category from other adrenocortical tumors. They are very rarely malignant. The majority have mutations that activate the Wnt/β-catenin signaling pathway, either in β-catenin itself, or in the **APC** gene, which regulates this pathway. Additional, somatic mutations are often found in the potassium channel, **KCNJ5**, which probably first causes cell hypertrophy (see Chapter 576.8).
579.1 Virilizing and Feminizing Adrenal Tumors
Perrin C. White

CLINICAL MANIFESTATIONS
Virilization is the most common presenting symptom in children with adrenocortical tumors, occurring in 50-80%. In males, the clinical picture is similar to that of simple virilizing congenital adrenal hyperplasia: accelerated growth velocity and muscle development, acne, penile enlargement, and the precocious development of pubic and axillary hair. In females, virilizing tumors of the adrenal gland cause masculinization of a previously normal female with clitoral enlargement, growth acceleration, acne, deepening of the voice, and premature pubic and axillary hair development.

Conversely, adrenal tumors can occasionally (less than 10%) secrete high levels of hormones as a result of overexpression of CYP19 (aromatase). Gynecomastia in males or premature thelarche in girls is often the initial manifestation. Growth and development may be otherwise normal, or concomitant virilization may occur.

In addition to virilization, 15-40% of children with adrenocortical tumors also have Cushing syndrome (see Chapter 577). Whereas isolated virilization occurs relatively frequently, children with adrenal tumors usually do not have Cushing syndrome alone.

In adults, adrenal tumors are frequently detected incident to CT or MRI imaging of the abdomen for other reasons; these are often referred to as incidentalomas (see Chapter 581.1). There are no published data on the frequency of the occurrence of such tumors in childhood. They are likely to be infrequent, being found in approximately 7% of autopsies of persons older than age 70 yr but in <1% of those younger than age 30 yr.

LABORATORY FINDINGS
Serum levels of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione are usually elevated, often markedly. Serum levels of testosterone are often increased, usually as a result of peripheral conversion of androstenedione, but infants with predominantly testosterone-secreting adrenomas have been reported. Levels of estrone and estradiol are elevated in tumors from patients with feminizing signs. Urinary 17-ketosteroids (sex steroid metabolites) are also increased but are no longer routinely measured. Many adrenocortical tumors have a relative deficiency of 11β-hydroxylase activity and secrete increased amounts of deoxycorticosterone; these patients are hypertensive, and their tumors are often malignant.

Tumors can usually be detected by ultrasonography, CT, or MRI. Preoperatively, the presence of metastatic disease should be determined by MRI or CT of the chest, abdomen, and pelvis. Radio-chemical imaging of these tumors by positron emission tomography with 11C-metomidate or single photon emission CT with 123I-iodometomidate have been proposed but are not routinely available.

PATHOLOGIC FINDINGS
Differentiation between benign and malignant tumors by histologic criteria (architecture, cytologic atypia, mitotic activity, atypical mitotic figures) is usually not possible; almost all pediatric adrenocortical tumors would be classified as malignant by the criteria used to classify adult tumors. Size is a useful prognostic factor, with tumors weighing less than 200 g, 200-400 g, and >400 g being classified as low, intermediate, and high risk (>10 cm diameter has also been suggested as a high-risk category). Incomplete resection and gross local invasion or metastasis are also associated with a poor prognosis. However, most tumors occurring in children younger than 4 yr of age fall into favorable prognostic categories.

DIFFERENTIAL DIAGNOSIS
For functioning tumors, the differential diagnoses are those of the main presenting signs and symptoms. The differential diagnosis for Cushing syndrome is discussed in Chapter 577. For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 576) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for hormonally inactive adrenocortical adenomas includes pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma (very rare in children). Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Not infrequently, a low level of autonomous cortisol secretion is detected that does not cause clinically apparent symptoms; this condition is sometimes referred to as "subclinical" Cushing syndrome.

TREATMENT
Functioning adrenocortical tumors should be removed surgically. There are no data on which to base a recommendation regarding non-functioning childhood incidentalomas; in adults, such tumors may be closely observed with imaging and repeat biochemical studies if smaller than 4 cm in diameter, but it is not certain that this is prudent in small children. Adrenalectomy may be performed either transperitoneally or laparoscopically. Some adrenocortical neoplasms are highly malignant and metastasize widely, but cure with regression of masculinizing or Cushingoid features may follow removal of less malignant, encapsulated tumors. Postoperatively, patients should be closely monitored biochemically, with frequent determinations of adrenal androgen levels and imaging studies. Recurrent symptoms or biochemical abnormalities should prompt a careful search for metastatic disease. Metastases primarily involve liver, lung, and regional lymph nodes. The majority of metastatic recurrences appear within 1 yr of tumor resection. Repeat surgical resection of metastatic lesions should be performed if possible and adjuvant therapy instituted. Radiation therapy has not been generally helpful. Antineoplastic agents such as cisplatin, etoposide, ifosfamide and carboplatin, and 5-fluorouracil and levamisole have had limited use in children, and their success is not established. Therapy with o,p′-DDD (mitotane), an adrenolytic agent, may relieve the symptoms of hypercortisolism or virilization in recurrent disease. Treatment with higher doses of mitotane for more than 6 mo is associated with improved survival. Other agents that interfere with adrenal steroid synthesis, such as ketoconazole, aminoglutethimide, and metyrapone, may also relieve symptoms of steroid excess but do not improve survival.

A neoplasm of 1 adrenal gland may produce atrophy of the other because excessive production of cortisol by the tumor suppresses adrenocorticotropic hormone stimulation of the normal gland. Consequently, adrenal insufficiency may follow surgical removal of the tumor. This situation can be avoided by giving 10-25 mg of hydrocortisone every 6 hr, starting on the day of operation and weaned over 3-4 days postoperatively. Adequate quantities of water, sodium chloride, and glucose also must be provided.

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


Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90%) is the adrenal medulla; however, tumors may develop anywhere along the abdominal sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation.
They also appear in the periadrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. Ten percent occur in children, in whom they present most frequently between 6 and 14 yr of age. Tumors vary from 1-10 cm in diameter; they are found more often on the right side than on the left. In more than 20% of affected children, the adrenal tumors are bilateral; in 30-40% of children, tumors are found in both adrenal and extradrenal areas or only in an extradrenal area.

ETIOLOGY
Pheochromocytomas may be associated with genetic syndromes such as von Hippel-Lindau disease, as a component of multiple endocrine neoplasia (MEN) syndromes MEN2A and MEN2B, and more rarely in association with neurofibromatosis (type 1) or tuberous sclerosis. The classic features of von Hippel-Landau syndrome, which occurs in 1 in 36,000 individuals, include retinal and central nervous system hemangioblastomas, renal clear cell carcinomas, and pheochromocytomas, but kindreds differ in their propensity to develop pheochromocytoma; in some kindreds, pheochromocytoma is the only tumor to develop. Germline mutations in the VHL tumor-suppressor gene on chromosome 3p25-26 have been identified in patients with this syndrome. Mutations of the RET protooncogene on chromosome 10q11.2 have been found in families with MEN2A and MEN2B. Patients with MEN2 are at risk of developing medullary thyroid carcinoma and parathyroid tumors; approximately 50% develop pheochromocytoma, with patients carrying mutations at codon 634 of the RET gene being at particularly high risk. Mutations are present in the NFI gene on chromosome 17q11.2 in neurofibromatosis type 1 patients.

Pheochromocytomas may occur in kindreds along with paragangliomas, particularly at sites in the head and neck. Such families typically carry mutations in the SDHB, SDHD, and, rarely, the SDHC genes encoding subunits of the mitochondrial enzyme succinate dehydrogenase.

Pheochromocytomas are also associated with tuberous sclerosis, Sturge-Weber syndrome, and ataxia-telangiectasia. Somatic mutations of the genes mentioned above, particularly VHL, have been found in some sporadic cases of pheochromocytoma (see Chapter 596).

CLINICAL MANIFESTATIONS
Pheochromocytomas detected by surveillance of patients who are known carriers of mutations in tumor-suppressor genes may be asymptomatic. Otherwise, patients are detected owing to hypertension, which results from excessive secretion of epinephrine and norepinephrine. All patients have hypertension at some time. Paroxysmal hypertension should particularly suggest pheochromocytoma as a diagnostic possibility, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When there are paroxysms of hypertension, the attacks are usually infrequent at first, but become more frequent and eventually give way to a continuous hypertensive state. Between attacks of hypertension, the patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Convulsions and other manifestations of hypertensive encephalopathy may occur. In severe cases, precordial pains radiate into the arms; pulmonary edema and cardiac and hepatic enlargement may develop. Symptoms may be exacerbated by exercise, or with use of nonprescription medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Growth failure may be striking. The blood pressure may range from 180-260 mm Hg systolic and from 120-210 mm Hg diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction.

LABORATORY FINDINGS
The urine may contain protein, a few casts, and occasionally glucose. Gross hematuria suggests that the tumor is in the bladder wall. Polycythemia is occasionally observed. The diagnosis is established by demonstration of elevated blood or urinary levels of catecholamines and their metabolites.

Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland. In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine. Total urinary catecholamine excretion usually exceeds 300 μg/24 hr. Urinary excretion of metanephrines (particularly normetanephrine) is also increased (see Fig. 574-3 in Chapter 574). Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured.

Elevated levels of free catecholamines and metanephrines can also be detected in plasma. In children, the best sensitivity and specificity are obtained by measuring plasma normetanephrine using gender-specific pediatric reference ranges, with plasma norepinephrine being next best. Plasma metanephrine and epinephrine are not reliably elevated in children. Additionally, the patient should be instructed to abstain from caffeinated drinks, and to avoid acetaaminophen, which can interfere with plasma normetanephrine assays. If possible, the blood sample should be obtained from an indwelling intravenous catheter, to avoid acute stress associated with venipuncture.

Most tumors in the area of the adrenal gland are readily localized by CT or MRI (Fig. 580-1), but extradrenal tumors may be difficult to detect. 123I-metaiodobenzylguanidaine is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors. Venous catherization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

DIFFERENTIAL DIAGNOSIS
Various causes of hypertension in children must be considered, such as renal or renovascular disease; coarctation of the aorta; hyperthyroidism; Cushing syndrome; deficiencies of 11β-hydroxylase, 17α-hydroxylase, or 11β-hydroxysteroid dehydrogenase (type 2 isozyme); primary aldosteronism; adrenocortical tumors; and, rarely, essential hypertension (see Chapter 445). A nonfunctioning kidney may result
from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders, diabetes insipidus, diabetes mellitus, and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma.

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neurogenic tumors often produce hypertension, excessive sweating, flushing, pallor, rash, polyuria, and polydipsia. Chronic diarrhea may be associated with these tumors, particularly with ganglioneuroma, and at times may be sufficiently persistent to suggest celiac disease.

**TREATMENT**

These tumors must be removed surgically, but careful preoperative, intraoperative, and postoperative management is essential. Preoperative α- and β-adrenergic blockade and fluid loading are required. Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Appropriate choice of anesthesia and expansion of blood volume with appropriate fluids during surgery are critical to avoid a precipitous drop in blood pressure during operation or within 48 hr postoperatively. Manipulation and excision of these tumors result in marked increases in catecholamine secretion that increase blood pressure and heart rate. Surveillance must continue postoperatively.

Although these tumors often appear malignant histologically, the only accurate indicators of malignancy are the presence of metastatic disease or local invasiveness that precludes complete resection, or both. Approximately 10% of all adrenal pheochromocytomas are malignant. Such tumors are rare in childhood; pediatric malignant pheochromocytomas occur more frequently in extraadrenal sites and are often associated with mutations in the SDHB gene encoding a subunit of succinate dehydrogenase. Prolonged follow-up is indicated because functioning tumors at other sites may be manifested many years after the initial operation. Examination of relatives of affected patients may reveal other individuals harboring unsuspected tumors that may be asymptomatic.

*Bibliography is available at Expert Consult.*
Bibliography
Adrenal masses are discovered with increasing frequency in patients undergoing abdominal imaging for reasons unrelated to the adrenal gland. The rate of detection of single adrenal masses has ranged from less than 1% to more than 4% of abdominal CT examinations in adults. The unexpected discovery of such a mass presents the clinician with a dilemma in terms of diagnostic steps to undertake and treatment interventions to recommend. The differential diagnosis of adrenal incidentaloma includes benign lesions such as cysts, hemorrhagic cysts, hematomas, and myelolipomas. These lesions can usually be identified on CT or MRI. If the nature of the lesion is not readily apparent, additional evaluation is required. Included in the differential diagnosis of lesions requiring additional evaluation are benign adenomas, pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma. Benign, hormonally inactive adrenocortical adenomas make up the majority of incidentalomas. Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Functional tumors require removal. If the adrenal mass is nonfunctional and larger than 4-6 cm, recommendations are to proceed with surgical resection of the mass. Lesions of 3 cm or less should be followed clinically with periodic reimaging. Treatment must be individualized; nonsecreting adrenal incidentalomas may enlarge and become hyperfunctioning. Nuclear scan, and occasionally fine-needle aspiration, may be helpful in defining the mass.

581.2 Adrenal Calcification

Calcification within the adrenal glands may occur in a wide variety of situations, some serious and others of no obvious consequence. Adrenal calcifications are often detected as incidental findings in radiographic studies of the abdomen in infants and children. The physician may elicit a history of anoxia or trauma at birth. Hemorrhage into the adrenal gland at or immediately after birth is probably the most common factor that leads to subsequent calcification (see Fig. 575-1 in Chapter 575). Although it is advisable to assess the adrenocortical reserve of such patients, there is rarely any functional disorder. Neuroblastomas, ganglioneuromas, cortical carcinomas, pheochromocytomas, and cysts of the adrenal gland may be responsible for calcifications, particularly if hemorrhage has occurred within the tumor. Calcification in such lesions is almost always unilateral.

In the past, tuberculosis was a common cause both of calcification within the adrenals and of Addison disease. Calcifications may also develop in the adrenal glands of children who recover from the Waterhouse-Friderichsen syndrome; such patients are usually asymptomatic. Infants with Wolman disease, a rare lipid disorder caused by a deficiency of lysosomal acid lipase, have extensive bilateral calcifications of the adrenal glands (see Chapter 86.4).

Bibliography is available at Expert Consult.
Bibliography

GENETIC CONTROL OF EMBRYONIC GONADAL DIFFERENTIATION

Gonadal differentiation is a complex, multistep process that requires the sequential action and interaction of multiple gene products.
Early in the 1st trimester, the undifferentiated, bipotential fetal gonad begins as a thickening of the urogenital ridge, near the developing kidney and adrenal cortex. At 6 wk of gestation, the gonad contains germ cells, stromal cells that will become Leydig cells in testes, or theca, interstitial, or hilar cells in the ovary; and supporting cells that will develop into Sertoli cells in testes or granulosa cells in ovaries. In males, SRY (sex-determining region on the Y chromosome) is transiently expressed, followed by a sequential upregulation of a number of testis-specific genes. SRY may also suppress a putative factor 2 that functions as a repressor of male development. In the absence of SRY, the bipotential gonad will be able to develop into an ovary. Ovarian development is also characterized by expression of ovary-specific genes during the same time period. One such gene is R-spondin1. During the gestation time period of 6-9 wk, a number of genes are upregulated to the same degree in both the testis and the ovary, including WNT4 and CTNNB1.

A chromosome complement of 46,XX is necessary for the development of normal ovaries. Both the long and short arms of the X chromosome contain genes for normal ovarian development. The DSS (dosage sensitive/sex reversal) locus associated with the DAX1 (DSS adrenal hypoplasia on the X chromosome) gene, which is defective in patients with X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism, is a member of the nuclear receptor superfamily and acts as a repressor of male gene expression. DAX1 acts by binding to a related nuclear receptor SF-1 (steroidogenic factor-1). In vitro, the signaling gene WNT4 stimulates expression of DAX1, resulting in the suppression of androgen synthesis in XX females. The WNTs are ligands that activate receptor-mediated signal transduction pathways and are involved in modulating gene expression as well as cell behavior, adhesion, and polarity. A key to its role in humans was elucidated by loss-of-function mutation of the WNT4 gene that was found in an 18 yr old 46,XX woman. She had absence of müllerian-derived structures (uterus and fallopian tubes), unilateral renal agenesis, and clinical signs of androgen excess.

Mutations of the Wilms tumor 1 (WT1) gene, including alternative splicing, may also impact sex differentiation. WT1 mutations are associated with the Denys-Drash syndrome (early-onset renal failure with abnormal external genitalia and Wilms tumor). Haploinsufficiency of a 3-amino-acid (KTS) form of WT1 has been implicated in the gonadal dysgenesis of patients with Fraser syndrome (late-onset progressive glomerulopathy and 46,XY gonadal dysgenesis). Mutations in the FOXL2 and SF-1 genes are associated with ovarian failure. Mutation of the R-spondin1 gene has been described in individuals with 46,XX DSD (disorder of sex development). Other autosomal genes also play a role in normal ovarian organogenesis and testicular development. Several conditions of gonadal dysgenesis are associated with gross abnormalities of both autosomes and sex chromosomes. A deletion affecting the short arm of the X chromosome produces the typical somatic anomalies of Turner syndrome.

Development of the testis requires the short arm of the Y chromosome; this contains the testis-determining factor SRY gene. During male meiosis, the Y chromosome must segregate from the X chromosome so that both X and Y chromosomes do not occur in the same spermatocyte. The major portion of the Y chromosome is composed of Y-specific sequences that do not pair with the X chromosome. However, a minor portion of the Y chromosome shares sequences with the X chromosome and pairing does occur in this region. The genes and sequences in this area recombine between the sex chromosomes, behaving like autosomal genes. Therefore, the term pseudoautosomal region is used to describe this portion of the chromosome, and the term indicates genetic behavior of these genes relative to pairing and recombination events. The SRY gene is localized to the 35-kb portion proximal to the pseudoautosomal region of the Y chromosome. It contains a high-mobility group (HMG) nonhistone protein (HMG box), supporting SRY’s role as a transcriptional regulator of other genes involved in sex differentiation. The gonadal ridge forms at around 33 days of gestation. SRY is detected at 41 days, peaks at 44 days when testis cords are first visible, and persists into adulthood.

Other genes that are found on autosomes are important in this process. SOX9, a SRY-related gene containing a region homologous with the HMG box 9 of SRY, is located on chromosome 17. Mutations of this gene result in XY sex reversal and campomelic dysplasia. SF-1 on chromosome 9q33 is important in adrenal and gonadal development, as well as the development of gonadotropin–releasing hormone–secreting neurons in the hypothalamus. WT1, especially the KST isoform on chromosome 11p13, is needed for early gonadal, adrenal, and renal development. Fibroblast growth factor-9, GATA-4, XH-2, and SOY9 are also important.

When genetic recombination events on sex chromosomes extend beyond the pseudoautosomal region, X- and Y-specific DNA may be transferred between the chromosomes. Such aberrant recombination results in X chromosomes carrying SRY, resulting in XX males, or Y chromosomes that have lost SRY, resulting in XY females. SRY acts as a transcriptional regulator to increase cellular proliferation, attract interstitial cells from adjacent mesonephros into the genital ridge, and stimulate testicular Sertoli cell differentiation. Sertoli cells act as an organizer of steroidogenic and germ cell lines and produce antimal-lerian hormone (AMH) that causes the female duct system to regress.

Table 582-1 lists additional genes involved in sex development.

Development of the ovary was once thought to be a passive process in the absence of SRY. Although the morphologic changes in the developing ovary are less marked than in the testis, there are a number of sequentially expressed genes and pathways that are required for complete ovarian development as well as maintenance of ovarian integrity postnatally. One of these genes is R-spondin1, which if mutated can result in testicular or ovotesticular development in 46,XX individuals. Some peptides in the Wnt-signaling pathway may antagonize testicular development. This effect may be mediated by β-catenin signaling, which is required for suppressing testicular features. Once developed, the ovary requires FAX12 to preserve its differentiation and stability.

FUNCTION OF THE TESTES

Levels of placental chorionic gonadotropin peak at 8-12 wk of gestation and stimulate the fetal Leydig cells to secrete testosterone, the main hormonal product of the testis. In the classical androgen biosynthetic pathway, testosterone is then converted by the enzyme 5α-reductase to its more potent metabolite, dihydrotestosterone. This early period is critical for normal and complete virilization of the XY fetus. Defects in this process lead to different forms of atypical male development (see Chapter 588.2). After virilization occurs, fetal levels of testosterone decrease but are maintained at lower levels in the latter half of pregnancy by luteinizing hormone (LH) secreted by the fetal pituitary; this LH-mediated testosterone secretion is required for continued penile growth, and to some degree also for testicular descent.

As part of the normal transition from intrauterine to extrauterine life, perhaps related to the sudden withdrawal of maternal and placental hormones, newborns and young infants experience a transient surge of gonadotropins and sex steroids. This is the so-called minipuberty.

In males, LH and testosterone peak at 1-2 mo of age and then decline to reach prepubertal levels by 4-6 mo of age. Follicle-stimulating hormone (FSH), along with inhibin B, peak at 3 mo and decline to prepubertal levels by 9 and 15 mo, respectively. The LH rise is more dominant than that of FSH.

The neonatal surge may be important for postnatal maturation of the gonads, stabilization of male external genitalia, and perhaps also for gender identity and sexual behaviors. The postnatal surge in LH and testosterone is absent or blunted in infants with hypopituitarism, cryptorchidism, and complete androgen insensitivity syndrome. The development of nocturnal pulsatile secretion of LH marks the advent of puberty.

Within specific target cells, 6-8% of testosterone is converted by 5α-reductase to dihydrotestosterone, a more potent androgen (Fig. 582-1), and approximately 0.3% is acted on by aromatase to produce estradiol. Approximately half of circulating testosterone is bound to sex hormone–binding globulin and half to albumin; only 2% circulates in the free form. Plasma levels of sex hormone–binding globulin are low at birth, rise rapidly during the 1st 10 days of life, and then remain stable until the onset of puberty. Thyroid hormone may play a role in this
### Table 582-1  Genes Known to Be Involved in Disorders of Sex Development (DSd)

<table>
<thead>
<tr>
<th>GENE</th>
<th>PROTEIN</th>
<th>OMIM DATA</th>
<th>LOCUS</th>
<th>INHERITANCE</th>
<th>GONAD</th>
<th>MÜLLERIAN STRUCTURES</th>
<th>EXTERNAL GENITALS</th>
<th>ASSOCIATED FEATURES/VARIANT PHENOTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorders of Gonadal (Testicular) Development: Single-Gene Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46,XY DSD</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT1</td>
<td>TF</td>
<td>607102</td>
<td>11p13</td>
<td>AD</td>
<td>Dysgenetic testis</td>
<td>±</td>
<td>Female or ambiguous</td>
<td>Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash, and Frasier syndromes)</td>
</tr>
<tr>
<td>SF-1 (NR5A1)</td>
<td>Nuclear receptor TF</td>
<td>184757</td>
<td>9q33</td>
<td>AD/AR</td>
<td>Dysgenetic testis</td>
<td>±</td>
<td>Female or ambiguous</td>
<td>More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis; mothers who carry SF-1 mutation have premature ovarian insufficiency</td>
</tr>
<tr>
<td>SRY</td>
<td>TF</td>
<td>480000</td>
<td>Yp11.3</td>
<td>Y</td>
<td>Dysgenetic testis</td>
<td>±</td>
<td>Female or ambiguous</td>
<td>Camptomelic dysplasia (17q24 rearrangements milder phenotype than point mutations)</td>
</tr>
<tr>
<td>SOX9</td>
<td>TF</td>
<td>608160</td>
<td>17q24-25</td>
<td>AD</td>
<td>Dysgenetic testis</td>
<td>±</td>
<td>Female or ambiguous</td>
<td>More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis; mothers who carry SF-1 mutation have premature ovarian insufficiency</td>
</tr>
<tr>
<td>DHH</td>
<td>Signaling molecule</td>
<td>605423</td>
<td>12q13.1</td>
<td>AR</td>
<td>Dysgenetic testis</td>
<td>+</td>
<td>Female</td>
<td>The severe phenotype of 1 patient included monofascicular neuropathy; other patients have isolated gonadal dysgenesis</td>
</tr>
<tr>
<td>ATRX</td>
<td>Helicase (?chromatin remodeling)</td>
<td>300032</td>
<td>Xq13.3</td>
<td>X</td>
<td>Dysgenetic testis</td>
<td>–</td>
<td>Female, ambiguous or male</td>
<td>S-α-Thalassemia, mental retardation</td>
</tr>
<tr>
<td>ARX</td>
<td>TF</td>
<td>3003382</td>
<td>Xp22.13</td>
<td>X</td>
<td>Dysgenetic testis</td>
<td>–</td>
<td>Ambiguous</td>
<td>X-linked lissencephaly, epilepsy, temperature instability</td>
</tr>
<tr>
<td><strong>Disorders of Gonadal (Testicular) Development: Chromosomal Changes Involving Key Candidate Genes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMRT1</td>
<td>TF</td>
<td>602424</td>
<td>9p24.3</td>
<td>Monosomic deletion</td>
<td>Dysgenetic testis</td>
<td>±</td>
<td>Female or ambiguous</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>DAXI (NR0B1)</td>
<td>Nuclear receptor TF</td>
<td>300018</td>
<td>Xp21.3</td>
<td>dupXp21</td>
<td>Dysgenetic testis</td>
<td>±</td>
<td>Female or ambiguous</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>WNT4</td>
<td>Signaling molecule</td>
<td>603490</td>
<td>1p35</td>
<td>dup1p35</td>
<td>Dysgenetic testis</td>
<td>+</td>
<td>Ambiguous</td>
<td>Leydig cell hypoplasia</td>
</tr>
<tr>
<td><strong>Disorders in Hormone Synthesis or Action</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LHGC</td>
<td>G-protein receptor</td>
<td>152790</td>
<td>2p21</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Female, ambiguous or micropenis</td>
<td>Smith-Lemli-Opitz syndrome: coarse facies, 2nd-3rd toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities</td>
</tr>
<tr>
<td>DHCR7</td>
<td>Enzyme</td>
<td>602858</td>
<td>11q12-13</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Variable</td>
<td>Smith-Lemli-Opitz syndrome: coarse facies, 2nd-3rd toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities</td>
</tr>
<tr>
<td>STAR</td>
<td>Mitochondrial membrane protein</td>
<td>600617</td>
<td>8p11.2</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Female</td>
<td>Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure</td>
</tr>
<tr>
<td>CYP11A1</td>
<td>Enzyme</td>
<td>118485</td>
<td>15q23-24</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Female or ambiguous</td>
<td>CAH (primary adrenal failure), pubertal failure</td>
</tr>
<tr>
<td>HSD3B2</td>
<td>Enzyme</td>
<td>201810</td>
<td>1p13.1</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Ambigious</td>
<td>CAH, primary adrenal failure, partial androgenization caused by 17,20-lyase deficiency</td>
</tr>
<tr>
<td>CYP17A1</td>
<td>Enzyme</td>
<td>202110</td>
<td>10q24.3</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Female or ambiguous</td>
<td>CAH, hypertension caused by 17α-hydroxylase deficiency, 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)</td>
</tr>
<tr>
<td>POR (P450 oxidoreductase)</td>
<td>CYP enzyme electron donor</td>
<td>124015</td>
<td>7q11.2</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Male or ambiguous</td>
<td>Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley-Bixler skeletal dysplasia</td>
</tr>
</tbody>
</table>

Continued
### Table 582-1  Genes Known to Be Involved in Disorders of Sex Development (DSD)—cont’d

<table>
<thead>
<tr>
<th>GENE</th>
<th>PROTEIN</th>
<th>OMIM DATA BASE NO.</th>
<th>LOCUS</th>
<th>INHERITANCE</th>
<th>GONAD</th>
<th>MÜLLERIAN STRUCTURES</th>
<th>EXTERNAL GENITALS</th>
<th>ASSOCIATED FEATURES/VARIANT PHENOTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSD17B3</td>
<td>Enzyme</td>
<td>605573</td>
<td>9q22</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Female or ambiguous</td>
<td>Partial androgenization at puberty, Tandrostenedione:testosterone ratio</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>Enzyme</td>
<td>607306</td>
<td>2p23</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Ambiguous or micropenis</td>
<td>Partial androgenization at puberty, Testosterone:DHT ratio</td>
</tr>
<tr>
<td>AMH</td>
<td>Signaling molecule</td>
<td>600957</td>
<td>19p13.3-13.2</td>
<td>AR</td>
<td>Testis</td>
<td>+</td>
<td>Normal male</td>
<td>PMDS; male</td>
</tr>
<tr>
<td>AMH-receptor</td>
<td>Serine-threonine</td>
<td>600956</td>
<td>12q13</td>
<td>AR</td>
<td>Testis</td>
<td>–</td>
<td>Normal male</td>
<td>External genitalia, bilateral cryptorchidism</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Nuclear receptor</td>
<td>3130700</td>
<td>Xq11-12</td>
<td>X</td>
<td>Testis</td>
<td>–</td>
<td>Female, ambiguous,</td>
<td>Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility</td>
</tr>
<tr>
<td>AKR1C2</td>
<td>3α-Hydroxysteroid</td>
<td>600450</td>
<td>10p15.1</td>
<td>AR</td>
<td>Testis</td>
<td>_</td>
<td>Female or female</td>
<td>Originally thought that affected members of this family had isolated 17,20-lyase deficiency (CYP17A1)</td>
</tr>
</tbody>
</table>

### 46,XX DSD Disorders of Gonadal (Ovarian) Development

<table>
<thead>
<tr>
<th>GENE</th>
<th>PROTEIN</th>
<th>OMIM DATA BASE NO.</th>
<th>LOCUS</th>
<th>INHERITANCE</th>
<th>GONAD</th>
<th>MÜLLERIAN STRUCTURES</th>
<th>EXTERNAL GENITALS</th>
<th>ASSOCIATED FEATURES/VARIANT PHENOTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRY</td>
<td>TF</td>
<td>480000</td>
<td>Yp11.3</td>
<td>Translocation</td>
<td>Testis or ovotestis</td>
<td>–</td>
<td>Male or ambiguous</td>
<td>Palmoplantar hyperkeratosis</td>
</tr>
<tr>
<td>SOX9</td>
<td>TF</td>
<td>608160</td>
<td>17q24</td>
<td>dup17q24</td>
<td>ND</td>
<td>Ovotestis</td>
<td>–</td>
<td>Male or ambiguous Amiguous</td>
</tr>
<tr>
<td>R-spondin 1</td>
<td>R-spondin</td>
<td>609595</td>
<td>1p34.3</td>
<td></td>
<td>Ovotestis</td>
<td></td>
<td></td>
<td>Palnnoplantar hyperkeratosis</td>
</tr>
<tr>
<td>HSD3B2</td>
<td>Enzyme</td>
<td>201810</td>
<td>1p13</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Clitoromegaly</td>
<td>CAH, primary adrenal failure, partial androgenization caused by TDEA</td>
</tr>
<tr>
<td>CYP21A2</td>
<td>Enzyme</td>
<td>201910</td>
<td>6p21-23</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td>CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, T17-hydroxyprogesterone</td>
</tr>
<tr>
<td>CYP11B1</td>
<td>Enzyme</td>
<td>20210</td>
<td>8q21-22</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td>CAH, hypertension caused by T11-deoxycortisol and 11-deoxyoicorticosterone</td>
</tr>
<tr>
<td>POR (P450 oxidoreductase)</td>
<td>CYP enzyme electron donor</td>
<td>124015</td>
<td>7q11.2</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td>Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; associated with Antley-Bixler skeletal dysplasia</td>
</tr>
<tr>
<td>CYP19</td>
<td>Enzyme</td>
<td>107910</td>
<td>15q21</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td>Maternal virilization during pregnancy, absent breast development at puberty, except in partial cases</td>
</tr>
<tr>
<td>Glucocorticoid receptor</td>
<td>Nuclear receptor</td>
<td>138040</td>
<td>5q31</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td>↑ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (patient heterozygous for a mutation in CYP21)</td>
</tr>
</tbody>
</table>

Chromosomal rearrangements likely to include key genes are included.

† Increased; ACTH, adrenocorticotropic; AD, autosomal dominant (often de novo mutation); AMH, antimüllerian hormone; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; DAX1, dosage sensitive/sex reversal adrenal hypoplasia on the X chromosome; DHEA, dehydroepiandrosterone; DHT, dehydrotestosterone; DSD, disorder of sex development; ND, not determined; PMDS, persistent müllerian duct syndrome; SF-1, steroidogenic factor-1; SRY, sex-determining region on the Y chromosome; StAR, steroidogenic acute regulatory; TF, transcription factor; WAGR, Wilms, aniridia, genital anomalies, and retardation; WT1, Wilms tumor 1; X, X-chromosomal; Y, Y-chromosomal.

physiologic increase because neonates with athyreosis (absence of the thyroid gland) have very low levels of sex hormone–binding globulin.

**AMH** (anti Müllerian hormone; previously referred to as *müllerian inhibitory substance*), **inhibin**, and **activin** are members of the transforming growth factor-β (TGF-β) superfamily of growth factors. This group, which has more than 45 members, also includes bone morphogenetic proteins. Members of the TGF-β superfamily are involved in the regulation of developmental processes and multiple diverse human disease states, including chondrodysplasias and cancer.

**AMH**, a homodimeric glycoprotein hormone encoded by a gene on chromosome 19, is the earliest secreted product of the Sertoli cells of the fetal testis. Produced as a prohormone, its carboxyterminal fragment is cleaved to make it active. AMH transcription is initiated by **SOX9** acting through the HMG box, while its expression is upregulated by **SF-1** binding to its promoter and further interacting with **SOX9**, **WT1**, and **GATA4**. AMH binds to 2 distinct serine/threonine receptors, each having a single transmembrane domain. The activated type 1 receptor signals to the SMAD family of intracellular mediators.
The gene for the AMH receptor (on chromosome 12) is expressed in Sertoli cells. In the female, it is expressed in fetal müllerian duct cells and in fetal and postnatal granulosa cells. During sex differentiation in males, AMH causes involution of the müllerian ducts, which are embryologic precursors of the cervix and uterus. It works in concert with SF-1 to cause involution of the fallopian tubes.

AMH is secreted in males by Sertoli cells during both fetal and postnatal life. In females, it is secreted by granulosa cells from 36 wk of gestation to menopause but at lower levels. The serum concentration of AMH in males is highest at birth, whereas in females it is highest at puberty. After puberty, both sexes have similar serum concentrations of AMH. Its role in postnatal life is not yet fully characterized.

Inhibin is another glycoprotein hormone secreted by the Sertoli cells of the testes and granulosa and theca cells of the ovary. Inhibin A consists of an α-subunit disulfide linked to the β-A subunit, whereas inhibin B consists of the same α subunit linked to the β-B subunit. Activins are dimers of the B subunits, either homodimers (BA/BA, BB/BB) or heterodimers (BA/BB). Inhibins selectively inhibit whereas activins stimulate pituitary FSH secretion. By means of immunooassays specific for inhibin A or B, it has been shown that inhibin A is absent in males and is present mostly in the luteal phase in women. Inhibin B is the principal form of inhibin in males and in females during the follicular phase. Inhibin B may be used as a marker of Sertoli cell function in males. FSH stimulates inhibin B secretion in females and males, but only in males is there also evidence for gonadotropin-independent regulation. Levels of inhibin B are currently being studied in children with various forms of gonalad and pubertal disorders. In males with delayed puberty, inhibin B may be a useful screening test to differentiate between constitutional delay of puberty and hypogonadotropic hypogonadism. In hypogonadotropic hypogonadism, the serum inhibin B level is very low to undetectable.

Like inhibin and activin, follistatin (a single-chain glycosylated protein) is produced by gonads and other tissues such as the hypothalamus, kidney, adrenal gland, and placenta. Follistatin inhibits FSH secretion principally by binding activins, thereby blocking the effects of activins at the level of both ovary and pituitary.

Many additional peptides act as mediators of the development and function of the testis. They include neurohormones such as growth hormone–releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, somatostatin, substance P, and neuropeptide Y; growth factors such as insulin-like growth factors and insulin-like growth factor–binding proteins, TGF-β, and fibroblast, platelet-derived, and nerve growth factors; vasoactive peptides; and immune-derived cytokines such as tumor necrosis factor and interleukins 1, 2, 4, and 6.

Clinical patterns of pubertal changes vary widely (see Chapters 14 and 561, covering pubertal maturation). In 95% of boys, enlargement of the genitals begins between 9.5 and 13.5 yr of age, reaching maturity at 13-17 yr of age. In a minority of normal boys, puberty begins after 15 yr of age. In some boys, pubertal development is completed in less than 2 yr, but in others it may take longer than 4.5 yr. Pubertal development and the adolescent growth spurt occur at an older age in boys than in girls.

The median age of sperm production (spermarche) is 14 yr. This event occurs in midpuberty as judged by pubic hair, testis size, evidence of growth spurt, and testosterone levels. Nighttime levels of FSH are in the adult male range at the time of spermarche; the first conscious ejaculation occurs at about the same time.

FUNCTION OF THE OVARIIES

In the normal female, the undifferentiated gonad can be identified histologically as an ovary by 10-11 wk of gestation, after the upregulation of R-spondin1. Oocytes are present from the 4th mo of gestation and reach a peak of 7 million by 5 mo of gestation. For normal maintenance, oocytes need granulosa cells to form primordial follicles. Functional FSH (but not LH) receptors are present in oocytes of primary follicles during follicular development. Normal X chromosomes are needed for maintenance of oocytes. In contrast to somatic cells, in which only 1 X chromosome is active, both Xs are active in germ cells. At birth, the ovaries contain approximately 1 million active follicles, which decrease to 0.5 million by menarche. Thereafter, they decrease at a rate of 1,000/mo, and at an even higher rate after the age of 35 yr.

The hormones of the fetal ovary are provided in most part by the fetoplacental unit. As in males, peak gonadotropin secretion occurs in fetal life and then again at 2-3 mo of life, with the lowest levels at about 6 yr of age. By contrast to males, the FSH surge predominates over LH in females. FSH peaks around 3-6 mo of age, declines by 12 mo, but remains detectable for 24 mo. Under LH influence, estradiol peaks at 2-6 mo of age. The inhibin B response is variable, peaking between 2 and 12 mo and remaining above prepubertal levels until 24 mo. In both infancy and childhood, gonadotropin levels are higher in females than in males.

The most important estrogens produced by the ovary are estradiol-17β (E2) and estrone (E1); estriol is a metabolic product of these 2, and all 3 estrogens may be found in the urine of mature females. Estrogens also arise from androgens produced by the adrenal gland and both the female and male gonads (see Fig. 574-1 in Chapter 574). This conversion explains why in certain types of disorders of sex differentiation in males, feminization occurs at puberty. In 17-ketosteroid reductase deficiency, for example, the enzymatic block results in markedly increased secretion of androstenedione, which is converted in the peripheral tissues to estradiol and estrone. These estrogens, in addition to those directly secreted by the testis, result in gynecomastia. Estradiol produced from testosterone in the complete androgen insensitivity syndrome causes complete feminization in XY individuals.

Estrogen regulates a host of functionally different activities in multiple tissues. There are at least 2 distinct estrogen receptors with different expression patterns. The ovary also synthesizes progesterone, the main progestational steroid; the adrenal cortex and testis also synthesize progesterone where it is a precursor for other adrenal and testicular hormones.

A host of other hormones with autocrine, paracrine, and intracrine effects have been identified in the ovary. They include inhibins, activins, relaxin, and growth factors insulin-like growth factor-1, TGF-α and TGF-β, and cytokines.

Plasma levels of estradiol increase slowly but steadily with advancing sexual maturation and correlate well with clinical evaluation of pubertal development, skeletal age, and rising levels of FSH. Levels of LH do not rise until secondary sexual characteristics are well developed. Estrogens, like androgens, inhibit secretion of both LH and FSH (negative feedback). In females, estrogens also provoke the surge of LH secretion that occurs in the mid–menstrual cycle. The capacity for this positive feedback is another maturational milestone of puberty.

The average age at menarche in American girls is approximately 12.5-13 yr; but the range of “normal” is wide, and 1-2% of normal girls have not menstruated by 16 yr of age. The age at onset of pubertal signs varies, with recent studies suggesting earlier ages than previously thought, especially in the U.S. African-American population (see Chapter 561). Menarche generally correlates closely with skeletal age. Maturation and closure of the epiphyses is at least partially estrogen dependent, as demonstrated by a very tall 28 yr old, normally masculinized male with continued growth as a result of incomplete closure of the epiphyses, who proved to have complete estrogen insensitivity caused by an estrogen-receptor defect.

DIAGNOSTIC TESTING

Improved, sensitive, and specific assays for pituitary and gonadal hormones that can be measured in small amounts of blood have contributed to rapid advances in the understanding of normal and abnormal hypothalamic-pituitary-gonadal interactions. In male infants, measurements of LH, FSH, and testosterone can detect pituitary and testicular defects. Leydig cell integrity in childhood can be determined by the testosterone response following human chorionic gonadotropin administration. (One protocol is to use 5,000 IU IM daily for 3 days; other protocols are available.) The integrity, as well as the maturity, of the hypothalamic-pituitary-gonadal axis in males and females can be assessed by measuring serial sex steroid, LH, and FSH levels after the subcutaneous administration of the gonadotropin-releasing hormone analog leuprolide. An ultrasensitive LH assay has been shown to
differentiate between boys with delayed puberty and those with complete, but not partial, hypogonadotropic hypogonadism. The normal range for inhibin B levels has been established in infant boys. Inhibin B may be a marker of spermatogenesis and also of tumors such as granulosa cell tumors. Inhibin may be involved in tumor suppression. Estrogen-receptor assays may be clinically useful in the management of various ovarian cancers. AMH measurements are useful in the evaluation of children with nonpalpable gonads and disorders of sex development.

**THERAPEUTIC USE OF SEX STEROIDS**

The estrogenic effects of polyhalogenated aromatic hydrocarbons may in part be a result of inhibition of estradiol sulfation by estrogen sulfotransferase, an important pathway of estradiol inactivation. Naturally occurring estrogens administered orally are rapidly destroyed by gastrointestinal and liver enzymes; accordingly, they are usually given as conjugates or esters. The most widely used oral preparations are equine conjugated estrogens (Premarin) and ethinyl estradiol. Estrogen-containing skin patches for transdermal absorption are also used. With improvements in the understanding of estrogen and estrogen-receptor interactions, a new class of compounds called *selective estrogen-receptor modulators* has been synthesized. For example, raloxifene, a nonsteroidal benzothiophene derivative, acts as an estrogen agonist in bone and liver and as an estrogen antagonist in breast and uterus.

Androgens, such as testosterone, are generally injected intramuscularly as long-acting esters (enanthate or cypionate, most commonly) because of their potency and steady response. Transdermal testosterone patches and a cutaneously applied gel have to date been used mostly in adults with hypogonadism because of the difficulty in titrating the doses needed during childhood and adolescence. Oral preparations, such as methyltestosterone or fluoxymesterone, do not produce so potent an androgenic response and may be hepatotoxic. Testosterone undecenoate, another oral preparation, is used in Europe but not in the United States. Sublingual (microspheres or pellets) and buccal (absorption via the buccal mucosa) preparations of testosterone are in development.

*Bibliography is available at Expert Consult.*
Chapter 582  Development and Function of the Gonads

Bibliography

Testicular hypofunction during fetal life can be a component of some types of disorders of sex development (see Chapter 588.2) and may lead to varying degrees of ambiguous genitalia. After birth, neonates undergo “minipuberty” with relatively high levels of gonadotropins and sex steroids, but this phenomenon is transient and its absence does not lead to any obvious clinical findings. Because prepubertal children normally do not produce significant amounts of testosterone and are not yet producing sperm, there are no discernible effects of testicular hypofunction in this age group. Testicular hypofunction from the age of puberty onward may lead to testosterone deficiency, infertility, or both. Such hypofunction may be primary in the testes (primary hypogonadism) or secondary to deficiency of pituitary gonadotropic hormones (secondary hypogonadism). Both types may be caused by inherited genetic defects or acquired causes, and in some cases the etiology may be unclear, but the level of the lesion (primary or secondary) is usually well defined; patients with primary hypogonadism have elevated levels of gonadotropins (hypergonadotropic); those with secondary hypogonadism have inappropriately low or absent levels of gonadotropins (hypogonadotropic). Table 583-1 details the etiologic classification of male hypogonadism.

**583.1 Hypergonadotropic Hypogonadism in the Male (Primary Hypogonadism)**

**ETIOLOGY**

Some degree of testicular function is essential in the development of phenotypically male newborns. If testicular function is present, sex differentiation is normally complete by the 14th wk of intrauterine life. Hypogonadism may occur after phenotypically male genitalia have developed for a variety of reasons; genetic or chromosomal anomalies may lead to testicular hypofunction that does not become apparent until the time of puberty, when these boys may have delayed or incomplete pubertal development. In other cases, normally developed testes may be damaged by infarction, trauma, radiation, chemotherapy, infections, infiltration, or other causes after sexual differentiation has occurred. In some cases, genetic defects may predispose to atrophy or maldescent; or torsion or infarction or may lead to progressive testicular damage and atrophy after a period of normal development. If testicular compromise is global, both testosterone secretion and fertility
(sperm production) are likely to be affected. Even when the primary defect is in testosterone production, low levels of intratesticular testosterone will frequently lead to infertility. The reverse is not necessarily true. Defects in sperm production and in the storage and transit of sperm may not be associated with low testosterone levels; infertility may thus be seen in patients with normal testosterone levels, normal libido, and normal secondary sexual characteristics.

Various degrees of primary hypogonadism also occur in a significant percentage of patients with chromosomal aberrations as in Klinefelter syndrome, males with more than one X chromosome, and XX male. These chromosomal anomalies are associated with other characteristic findings. Noonan syndrome is associated with cryptorchidism and infertility, but other (nongonadal) features dominate its clinical picture.

**Congenital Anorchia or Testicular Regression Syndrome**

Boys in whom the external genitalia have developed normally (or nearly normally) and müllerian duct derivatives (uterus, fallopian tubes) are absent have obviously had testicular function for at least some part of gestation. If their testes cannot be palpated at birth, they are said to have cryptorchidism. In most such cases, the testes are undescended or retractile, but in some cases no testes are found in any location, even after extensive investigation. This syndrome of absence of testes in a phenotypic male with normal 46,XY karyotype (indicating that there was some period of testicular function in intrauterine life) is known as “vanishing testes,” “congenital anorchia,” or “testicular regression syndrome.”

Testicular regression syndrome is not uncommon. Cryptorchidism occurs in 1.5–9% of male births and in 10–20% of these cases, the testes are impalpable. Of children with impalpable testes, up to 50% may have no detectable testes after extensive investigation. Most cases appear to be sporadic and are thought to be a result of torsion or vascular accidents. The incompletely descended testis may be more prone to torsion and this may be one of the causes of “vanishing testes.” Most cases are sporadic but in a subset of patients testicular regression syndrome occurs in monozygotic twins or in families with other affected individuals, suggesting a genetic etiology. Some cases are associated with microopenis and in these cases the testicular loss probably occurred after the 14th wk, but well before the time of birth, or this may indicate a preexisting dysfunction of male hormonal development. Low levels of testosterone (<10 ng/dL) and markedly elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are found in the early postnatal months; thereafter, levels of gonadotropins tend to decrease even in agonal children, rising to very high levels again as the pubertal years approach. Stimulation with human chorionic gonadotropin (hCG) fails to evoke an increase in the level of testosterone. Serum levels of antimullerian hormone (AMH) are undetectable or low. All patients with undetectable testes should be tested for AMH and should undergo an hCG stimulation test. If the results indicate that no testicular tissue is present (absent AMH and no rise in testosterone after hCG stimulation), then the diagnosis of testicular regression syndrome is confirmed. If testosterone secretion is demonstrated, then imaging with abdominal MRI or/surgical exploration is indicated. A small fibrotic nodule may be found at the end of the spermatic cord in many cases of testicular regression syndrome. Treatment of male hypogonadism (primary or secondary) is discussed in Chapter 583.2. There is no possibility of normal fertility in these patients.

**Chemotherapy and Radiation-Induced Hypogonadism**

Testicular damage is a frequent consequence of chemotherapy and radiotherapy for cancer. The frequency and extent of damage depend on the agent used, total dose, duration of therapy, and posttherapy interval of observation. Another important variable is age at therapy; germ cells are less vulnerable in prepubertal than in pubertal and postpubertal boys. Chemotherapy is most damaging if more than 1 agent is used. The use of alkylating agents such as cyclophosphamide in prepubertal children does not impair pubertal development, even though there may be biopsy evidence of germ cell damage. High doses of cyclophosphamide and ifosfamide are associated with infertility. Cisplatin causes transient azoospermia or oligospermia at lower doses, while higher doses (400–600 mg/m²) can cause permanent infertility. Interleukin 2 can depress Leydig cell function, whereas interferon-α does not seem to affect gonadal function. Most chemotherapeutic agents produce azoospermia and infertility; Leydig cell damage (leading to low testosterone levels) is less common. In many cases, the damage is transient and sperm counts recover after 12–24 mo. Both chemotherapy and radiotherapy are associated with an increase in the percentage of abnormal gametes, but data concerning the outcomes of pregnancies after such therapy have not shown any increase in genetically mediated birth defects, possibly because of selection bias against abnormal sperm.

**Radiation damage** is dose dependent. Temporary oligospermia can be seen with doses as low as 0.1 Gy, with permanent azoospermia seen with doses greater than 2 Gy. Recovery of spermatogenesis can be seen as long as 5 yr (or more) after irradiation, with higher doses leading to slower recovery. Leydig cells are more resistant to irradiation. Mild damage as determined by elevated LH levels can be seen with up to 6 Gy; doses greater than 30 Gy cause hypogonadism in most patients. Whenever possible, testes should be shielded from irradiation. Testicular function should be carefully evaluated in adolescents after multimodal treatment for cancer in childhood. Replacement therapy with testosterone and counseling concerning fertility may be indicated. The storage of sperm prior to chemotherapy or radiation treatment in postpubertal males is an option. Even in those cases where sperm counts are abnormal, recovery is possible, though the chances of recovery decline with increasing dose of radiation. If sperm counts remain low, fertility is still possible in some cases with testicular sperm extraction and intracytoplasmic sperm injection.

**Sertoli Cell–Only Syndrome**

Small testes and azoospermia are seen in patients with the extremely rare Sertoli cell–only syndrome (germ cell aplasia, or Del Castillo syndrome). These patients have no germ cells in the testes, but usually have normal testosterone production, and present as adults with the complaint of infertility. Most cases are sporadic and idiopathic, but deletions involving the azoospermia factor (AZF) region of the Y chromosome (Yq11) may be found in some cases.

**Other Causes of Testicular Hypofunction**

Atrophy of the testes may follow damage to the vascular supply as a result of manipulation of the testes during surgical procedures for correction of cryptorchidism or as a result of bilateral torsion of the testes. **Acute orchitis** is common in pubertal or adult males with mumps and may lead to subfertility in 13% of cases, though infertility is rare. Testosterone secretion usually remains normal. The incidence of mumps orchitis in postpubertal males has increased in some areas as a result of decrease in measles, mumps, and rubella vaccination uptake. Autoimmune polyendocrinopathy may be associated with primary hypogonadism (associated with anti-P450scx antibodies) but this appears to be more common in females.

**Testicular Dysgenesis Syndrome**

The incidence of testicular cancer has increased in many developed societies while the incidence of cryptorchidism, hypospadias, low sperm counts, and sperm abnormalities also appears to have increased in some, but not all, studies. It has been proposed that all these trends are linked by prenatal testicular dysgenesis. The hypothesis is that some degree of testicular dysgenesis develops in intrauterine life from genetic as well as environmental factors, and is associated with increased risk of cryptorchidism, hypospadias, hypofertility, and testicular cancer. The environmental influences that have been implicated in this syndrome include environmental chemicals that act as endocrine disruptors, such as bisphenol A and phthalates (components of many types of plastics), several pesticides, phytoestrogens or mycoestrogens, and other chemicals. The fact that these lesions can be reproduced in some animal models by environmental chemicals has led to efforts to remove...
these chemicals from products used by infants and pregnant mothers, and from the environment in general. Nonetheless, the evidence is only suggestive and is not conclusive.

**CLINICAL MANIFESTATIONS**

Primary hypogonadism may be suspected at birth if the testes and penis are abnormally small. Normative data are available for different populations. The condition often is not noticed until puberty, when secondary sex characteristics fail to develop. Facial, pubic, and axillary hair is scant or absent; there is neither acne nor regression of scalp hair; and the voice remains high pitched. The penis and scrotum remain infantile and may be almost obscured by pubic fat; the testes are small or not palpable. Fat accumulates in the region of the hips and buttocks and sometimes in the breasts and on the abdomen. The ephipyses close later than normal; therefore, extremities are long. The span may be several inches longer than the height, and the distance from the symphysis pubis to the soles of the feet (lower segment) is much greater than that from the symphysis to the vertex (upper segment). The proportions of the body are described as eunuchoid. The upper to lower segment ratio is considerably less than 0.9. Many individuals with milder degrees of hypogonadism may be detected only by appropriate studies of the pituitary-gonadal axis. Examination of the testes should be performed routinely by pediatricians; testicular volumes as determined by comparison with standard orchidometers or by measurement of linear dimensions should be recorded.

**DIAGNOSIS**

Levels of serum FSH and, to a lesser extent, of LH are elevated to greater than age-specific normal values in early infancy (when “mini-puberty” normally occurs and the gonadotropins are normally disinhibited). This is followed by a period of time when even agonal children may not exhibit significant elevation in gonadotropins, indicating that the gonadotropins are also suppressed at this stage by some mechanism independent of feedback inhibition by gonadal hormones. In the latter half of childhood and several years prior to the onset of puberty, this inhibition is released and gonadotropin levels again rise above age-matched normals in subjects with primary hypogonadism. These elevated levels indicate that even in the prepubertal child there is an active hypothalamic-gonadal feedback relationship. After the age of 11 yr, FSH and LH levels rise significantly, reaching the castrate range. Measurements of random plasma testosterone levels in prepubertal boys are not helpful because they are ordinarily low in normal prepubertal children, rising during puberty to attain adult levels. During puberty, these levels, when measured in an early-morning blood sample, correlate better with testicular size, stage of sexual maturity, and bone age than with chronological age. In patients with primary hypogonadism, testosterone levels remain low at all ages. There is an attenuated rise or no rise at all after administration of hCG, in contrast to normal males in whom hCG produces a significant rise in plasma testosterone at any stage of development.

AMH is secreted by the Sertoli cells and this secretion is suppressed by testosterone. As a result, AMH levels are elevated in prepubertal boys and suppressed at onset of puberty. Boys with primary hypogonadism continue to have elevated AMH levels in puberty. Detection of AMH may be used in prepubertal years as an indicator of the presence of testicular tissue (e.g., in patients with bilateral cryptorchidism). Inhibin B is also secreted by the Sertoli cells, is present throughout childhood, and rises at onset of puberty (more in boys than in girls). It may be used as another marker of the presence of testicular tissue in bilateral cryptorchidism and as a marker of spermatogenesis (e.g., in delayed puberty, cancer survivors, and patients with Noonan syndrome). Bone age x-rays are useful to document delayed bone age in patients with constitutional growth delay as well as primary hypogonadism.

**NOONAN SYNDROME**

**Etiology**

The term Noonan syndrome has been applied to males and females with normal karyotypes who have certain phenotypic features that occur also in females with Turner syndrome (although the genetic causes are completely distinct) (see Chapter 81.4). Noonan syndrome occurs in 1 in 1,000-2,500 live births. Approximately 20% of the cases are familial and exhibit autosomal dominant inheritance. Males and females are equally affected. It is now thought that several mutations in the renin–angiotensin system (RAS)–mitogen-activated protein kinase (MAPK) pathway can cause Noonan syndrome and other related disorders and such mutations are currently detected in approximately 70% of the cases of Noonan syndrome. Missense mutations in *PTPN11*—a gene on chromosome 12q24.1 encoding the nonreceptor protein tyrosine phosphatase SHP-2—are seen in about half the cases. Mutations in other genes in this pathway, including *SHOC2, CBL, SOS1, KRAS, NRAS, BRAF, and RAF1*, as well as duplications of the 12q24 region, are also seen. Phenotypic features of Noonan syndrome therefore overlap with other syndromes involving the RAS-MAPK pathway, such as Leopard syndrome and cardiofaciocutaneous syndrome.

**Clinical Manifestations**

The most common abnormalities are short stature, webbing of the neck, pectus carinatum or pectus excavatum, cubitus valgus, right-sided congenital heart disease, and characteristic facies. Hypertelorism, epicanthus, downward-slanting palpebral fissures, ptosis, micrognathia, and ear abnormalities are common. Other abnormalities such as clinodactyly, hernias, and vertebral anomalies occur less frequently. As opposed to Turner syndrome, the mean IQ of school-age children with Noonan syndrome is subnormal at 86, with a range of 53-127. Verbal IQ tends to be better than performance IQ. High-frequency sensorineural hearing loss is common. The cardiac defect is most often pulmonary valvular stenosis, hypertrophic cardiomyopathy, or atrial septal defect. Hepatosplenomegaly and several hematologic diseases, including low clotting factors XI and XII, acute lymphoblastic leukemia, and chronic myelomonocytic leukemia, are noted. Noonan-like features can be part of the phenotypic variation of the *NFI* (neurofibromatosis) gene mutation, possibly as a result of common involvement of the RAS-MAPK pathway in both diseases. Males frequently have cryptorchidism and small testes. Testosterone secretion may be low or normal, but spermatogenesis may be affected even in those with normal testosterone (and normal secondary sexual characteristics). Serum inhibin-B is a useful marker of Sertoli cell function in these patients. Puberty is delayed and adult height is achieved by the end of the 2nd decade and usually reaches the lower limit of the normal population. Prenatal diagnosis should be suspected in fetuses with normal karyotype, edema, or hydrops and short femur length.

**Treatment**

Human growth hormone results in improvement in growth velocity in many Noonan syndrome patients, comparable to that seen in patients with Turner syndrome, and studies show a mean increase in height standard deviation score ranging from 1.3–1.7, corresponding to 9.5-13 cm for boys and 9.0-9.8 cm for girls. Many patients with Noonan syndrome reach normal height without growth hormone therapy, but treatment is recommended for those who fall below the 3rd percentile for height. The recommended dose is up to 66 µg/kg/day of recombinant growth hormone. Patients with Noonan syndrome and demonstrable *PTPN11* mutations grow less well and are less responsive to growth hormone treatment than those without mutations. They have lower insulin-like growth factor-1 and higher growth hormone levels, suggesting partial growth hormone resistance because of post–receptor-signaling defects. Treatment of male hypogonadism is discussed in Chapter 583.2.

**KLINEFELTER SYNDROME**

See also Chapter 81.

**Etiology**

Klinefelter syndrome is the most common sex chromosomal aneuploidy in males, with an incidence of 0.1-0.2% in the general population (1 in 500-1,000) and rising to 4% among infertile males and 10-11% in those with oligospermia or azoospermia. Approximately 80% of them have a 47,XXX chromosome complement, while mosaics...
and higher degrees of polyX are seen in the remaining 20%. Even with as many as 4 X chromosomes, the Y chromosome determines a male phenotype. The chromosomal aberration most often results from meiotic nondisjunction of an X chromosome during parental gametogenesis; the extra X chromosome is maternal in origin in 54% and paternal in origin in 46% of patients. A national study in Denmark revealed a prenatal prevalence of 213 per 100,000 male fetuses, but in adult men the prevalence was only 40 per 100,000, suggesting that only 1 in 4 of adult males with Klinefelter syndrome was diagnosed.

**Clinical Manifestations**

In patients who do not have a prenatal diagnosis, the diagnosis is rarely made before puberty because of the paucity or subtlety of clinical manifestations in childhood. Behavioral or psychiatric disorders may be apparent long before defects in sexual development. These children tend to have learning disabilities and deficits in “executive function” (concept formation, problem solving, task switching, and planning), and the condition should be considered in boys with psychosocial, learning, or school adjustment problems. Affected children may be anxious, immature, or excessively shy and tend to have difficulty in social interactions throughout life. In a prospective study, a group of children with 47.XXY karyotypes identified at birth exhibited relatively mild deviations from normal during the 1st 5 yr of life. None had major physical, intellectual, or emotional disabilities; some were inactive, with poorly organized motor function and mild delay in language acquisition. Problems often first become apparent after the child begins school. Full-scale IQ scores may be normal, with verbal IQ being somewhat decreased. Verbal cognitive defects and underachievement in reading, spelling, and mathematics are common. By late adolescence, many boys with Klinefelter syndrome have generalized learning disabilities, most of which are language based. Despite these difficulties, most complete high school.

The patients tend to be tall, slim, and have a specific tendency to have long legs (disproportionate to the arms, and longer than those seen with other causes of hypogonadism), but body habitus can vary markedly. The testes tend to be small for age, but this sign may become apparent only after puberty, when normal testicular growth fails to occur. The phallus tends to be smaller than average, and cryptorchidism is more common than in the general population. Bone mineral density may be low in adults with Klinefelter syndrome and this correlates with lower testosterone levels.

Pubertal development may be delayed, although some children undergo apparently normal or nearly normal virilization. Despite normal testosterone levels, serum LH and FSH concentrations and their responses to gonadotropin-releasing hormone (GnRH) stimulation are elevated starting at around 13 yr of age. Approximately 80% of adults have gynecomastia; they have sparser facial hair, most shaving less often than daily. The most common testicular lesions are seminiferous tubular atrophy and Sertoli cell predominance. The sperm have a density may be low in adults with Klinefelter syndrome and this correlates with lower testosterone levels.

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There are an increased incidence in adulthood of central adiposity, metabolic syndrome, pulmonary disease, varicose veins, and cancer of the breast. Among 93 unselected male breast cancer patients, 7.5% were found to have Klinefelter syndrome. Mediastinal germ cell tumors have been reported; some of these tumors produce hCG and cause precocious puberty in young boys. They may also be associated with leukemia, lymphoma, and other hematologic neoplasia. The highest cancer risk (relative risk: 2.7) occurs in the 15–30 yr age group. A large cohort study in Britain demonstrated an overall significantly increased standardized mortality ratio (1.5), with particular increases in deaths from diabetes, epilepsy, peripheral and intestinal vascular sufficiency, pulmonary embolism, and renal disease. Mortality from ischemic heart disease was decreased. In adults, structural brain abnormalities correlate with cognitive deficits.

In adults with XY/XXY mosaicism, the features of Klinefelter syndrome are decreased in severity and frequency. Children with mosaicism have a better prognosis for virilization, fertility, and psychosocial adjustment.

**Klinefelter Variants and Other Poly-X Syndromes**

When the number of X chromosomes exceeds 2, the clinical manifestations, including mental retardation and impairment of virilization, are more severe. Height decreases with increasing number of X chromosomes. The XXY variant is the most common variant (1 in 18,000–40,000 male births). In most, mental retardation occurs with IQ scores between 60 and 80, but 10% have IQs greater than 110. The XXY male phenotype is not distinctively different from that of the XXY patient, except that XXY adults tend to be taller than the average XXY patient. The 49,XXXXY variant is sufficiently distinctive to be detected in childhood. Its incidence is estimated to be 1 in 80,000–100,000 male births. The disorder arises from sequential nondisjunction in meiosis. Affected patients are severely cognitively impaired and have short necks and typical coarse facies with wide-set eyes with a mild upward slant of the fissures, epicanthus, strabismus, a wide and flat upturned nose, a large open mouth, and large malformed ears. The testes are small and may be undescended, the scrotum is hypoplastic, and the penis is very small. Defects suggestive of Down syndrome (short, incurved terminal 5th phalanges, single palmar creases, and hypotonia) and other skeletal abnormalities (including defects in the carrying angle of the elbows and restricted supination) are common. The most frequent radiographic abnormalities are radioulnar synostosis or dislocation, elongated radius, pseudoepiphyses, scoliosis or kyphosis, coxa valga, and retarded osseous age. Most patients with such extensive changes have a 49,XXXXY chromosome karyotype; several mosaic patterns have also been observed: 48,XXX/49,XXXXY; 48,XXXXY/49,XXXXY/50,XXXXXY; and 48,XXXYY/49,XXXYY/50,XXXXXY. Prenatal diagnosis of a 49,XXXXY infant has been reported. The fetus had intrauterine growth retardation, edema, and cystic hygroma coli. The 48,XXXYY variant is relatively rare. The characteristic features are generally less severe than those of patients with 49,XXXXY and more severe than those of 47,XXX patients. Mild intellectual disability, delayed speech and motor development, and immature but passive and pleasant behavior are associated with this condition.

Very few patients have been described with 49,XXYY and 49,XXYY karyotypes. Dysmorphic features and cognitive impairment are common to both.

**Laboratory Findings**

Most males with Klinefelter syndrome go through life undiagnosed. The chromosomes should be examined in all patients suspected of having Klinefelter syndrome, particularly those attending child guidance, psychiatric, and cognitive disability clinics. In infancy, inhibin B and AMH levels are normal but testosterone levels are lower than in controls. Before 10 yr of age, boys with 47,XXX Klinefelter syndrome have normal basal plasma levels of FSH and LH. Responses to gonadotropin-stimulating hormone and to hCG are normal. The testes show normal growth early in puberty, but midpuberty the testicular growth stops, gonadotropins become elevated, and testosterone levels are slightly low. Inhibin B levels are normal in early puberty, decrease in late puberty, and are low in adults with the syndrome. Elevated levels of estradiol, resulting in a high estradiol to testosterone ratio, account for the development of gynecomastia during puberty. Sex hormone–binding globulin levels are elevated, further decreasing free testosterone levels. Long androgen receptor polyglutamine (CAG) repeat length is associated with the more-severe phenotype, including gynecomastia, small testes, and short penile length.

Testicular biopsy before puberty may reveal only deficiency or absence of germinal cells. After puberty, the seminiferous tubular membranes are hyalinized, and there is adenomatous clumping of Leydig cells. Sertoli cells predominate. Azospermia is characteristic, and infertility is the rule.
Management

Boys known to have Klinefelter syndrome should be monitored closely for speech, learning, and behavioral problems, and referred for early evaluation and treatment as needed. Testosterone, LH, and FSH levels should be checked at 11-12 yr of age and replacement therapy with a testosterone preparation is recommended once FSH and LH begin to rise above normal. Fasting glucose, lipids, and hemoglobin A1c should also be obtained as these children are at risk for central adiposity and metabolic syndrome. A baseline dual-energy x-ray absorptiometry scan to assess bone density is also recommended by some authorities. Although testosterone treatment will normalize testosterone levels, stimulate the development of secondary sexual characteristics, increase bone mass and muscle mass, and improve body composition, it will not improve fertility (and will, in fact, suppress spermatogenesis).

There is some evidence that it also improves mood and may have a positive effect on cognition and social functioning but the findings are not conclusive at this time. Either long-acting testosterone injections or daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are not frequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly every 3-4 wk, with 50-mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosterone one patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone one may also be used as initial treatment instead of injections. For older boys, larger initial doses and increments can achieve more rapid virilization. The various transdermal preparations differ somewhat from each other and standard references should be consulted for recommendations regarding dosage and mode of application.

Gynecomastia may be treated with aromatase inhibitors (which will also increase endogenous testosterone levels) but medical treatment is not always successful and plastic surgery may be needed. Fertility is usually not an issue in the pediatric age group, but adults can father children using testicular sperm extraction followed by intracytoplasmic sperm injection. Because sperm counts decrease rapidly after onset of puberty in children with Klinefelter syndrome, sperm banking during early puberty is an option that can be discussed with a fertility specialist. Sperm counts can be stimulated using hCG treatment prior to testicular sperm extraction. Therapy, counseling and psychiatric services should be provided as needed for learning difficulties and psychosocial disabilities.

**XX MALES**

This disorder is thought to occur in 1 in 20,000 newborn males. Affected individuals have a male phenotype, small testes, a small phallus, and no evidence of ovarian or müllerian duct tissue. They appear, therefore, to be distinct from the oovesticular disorder of sexual development. Undescended testes and hypospadias occur in a minority of patients. Infertility occurs in practically all cases and appears, therefore, to be distinct from the ovotesticular disorder of sexual development. In a starting dose of 25-50 mg injected intramuscularly every 3-4 wk, with 50-mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosteronone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older boys, larger initial doses and increments can achieve more rapid virilization. The various transdermal preparations differ somewhat from each other and standard references should be consulted for recommendations regarding dosage and mode of application.

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**45,X MALES**

In a few male patients recognized with a 45,X karyotype, Yp sequences are translocated to an autosomal chromosome. In 1 instance, the terminal short arm of the Y chromosome was translocated onto an X chromosome. In another, SRY/autosomal translocation was postulated. A male with 45,X karyotype and Leri-Weill dyschondrosteosis, SHOX gene loss, and SRY to Xp translocation also has been described.

**47,XXX MALES**

A Japanese male with poor pubic hair development, hypoplastia scrotal testes (4 mL), normal penis and normal height, gynecomastia, and severe cognitive impairment had 47,XXX karyotype caused by an abnormal X-Y interchange during paternal meiosis and X-X nondisjunction during maternal meiosis.

*Bibliography is available at Expert Consult.*

**583.2 Hypogonadotropic Hypogonadism in the Male (Secondary Hypogonadism)**

Omar Ali and Patricia A. Donohoue

In hypogonadotropic hypogonadism, lack of gonadal function is secondary to deficiency of 1 or both gonadotropins: FSH or LH. The primary defect may lie either in the anterior pituitary or in the hypothalamus. Hypothalamic etiologies result in deficiency of GnRH. The tests are normal but remain in the prepubertal state because stimulation by gonadotropins is lacking. The disorder may be recognized in infancy but is much more commonly recognized because of marked pubertal delay. Rarely, patients with an inherited form of hypogonadotropic hypogonadism (HH) may go through puberty and may present with hypogonadism as adults.

**ETIOLOGY**

HH may be genetic or acquired. Several different genes can cause inherited forms of HH; the affected genes may be upstream of GnRH, at the level of GnRH receptors, or at the level of gonadotropin production. In addition, various genetic defects in transcription factors such as POUF-1, LHX-3, LHX-4, and HESX-1 lead to defects in pituitary development and multiple pituitary hormone deficiencies, including deficiency of gonadotropins. Acquired pituitary gonadotropin deficiency may develop from various lesions in the hypothalamic-pituitary region (e.g., tumors, infiltrative disease, autoimmune disease, trauma, stroke).

**Isolated Gonadotropin Deficiency**

Isolated gonadotropin deficiency in which other pituitary hormone levels are normal is more likely to be from defects in the secretion of GnRH from the hypothalamus rather than defects in gonadotropin synthesis in the pituitary. It affects approximately 1 in 10,000 males and 1 in 50,000 females and encompasses a heterogeneous group of entities. Many cases are associated with anosmia and this combination of anosmia and HH defines Kallmann syndrome.

**Kallmann syndrome** is the most common form of HH and is genetically heterogeneous, with autosomal recessive, X-linked, and autosomal dominant forms of inheritance. Clinically, it is characterized by its association with anosmia or hyposmia; 85% of the cases are autosomal and 15% are X-linked. The X-linked form (KAL1) is caused by mutations of the KAL1 gene at Xp22.3. This leads to failure of olfactory axons and GnRH-expressing neurons to migrate from their common origin in the olfactory placode to the brain. The KAL1 gene product anosmin-1, an extracellular 95 kDa matrix glycoprotein, facilitates neuronal growth and migration. The KAL1 gene is also expressed in various parts of the brain, facial mesenchyme, and mesonephros and metanephros, thus explaining some of the associated findings in patients with Kallmann syndrome, such as synkinesia (mirror movements), hearing loss, midfacial defects, and renal agenesis.

Some kindreds contain anosmic individuals with or without hypogonadism; others contain hypogonadal individuals who are anosmic.
Bibliography


Cleft lip and palate, hyiptelorism, median facial clefts, sensorineural hearing loss, unilateral renal aplasia, neurologic deficits, and other findings occur in some affected patients. When Kallmann syndrome is caused by terminal or interstitial deletions of the Xp22.3 region, it may be associated with other contiguous gene syndromes, such as steroid sulfatase deficiency, chondrodysplasia punctata, X-linked ichthyosis, or ocular albinism.

The autosomal dominant form of Kallmann syndrome (KAL2) occurs in up to 10% of patients, and is caused by a loss of function mutation in the fibroblast growth factor receptor 1 (FGFR1) gene. Cleft lip and palate are associated with KAL2 but not with KAL1. Oligodontia and hearing loss may occur with both KAL1 and KAL2.

A variety of other genes, including FGFR8, PROK2/PROKR2, NELF, CHD7 (responsible for CHARGE [coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies] syndrome, which includes hypogonadism in its phenotype), HS6ST1, WDR11, and SEMA3A, are associated with defects in neuronal migration that can result in Kallmann syndrome, but in most patients the affected gene remains undefined.

**Hypogonadotropic Hypogonadism Without Anosmia**

A specific genetic defect is not found in most cases of normosmic idiopathic hypogonadotropic hypogonadism (IHH) but the list of genes associated with this disorder is growing; mutations in the genes KISS1/KISS1R, TAC3/TACR3, and GNRH1/GNRHR lead to abnormalities in the secretion and action of GnRH and are seen exclusively in patients with normosmic IHH. Mutations in FGFR1, FGFR8, CHD7, and WDR11 more commonly present with anosmia/hyposmia (Kallmann syndrome), but are also associated with normosmic IHH in some cases. It appears that kisspeptin (the gene product of the KISS1 gene) and its G-protein–coupled receptor (GPCR54) play an important role in triggering puberty in humans and act downstream of the leptin receptor in this pathway. Rare cases of leptin deficiency and leptin receptor defects are also associated with IHH. In addition, starvation and anorexia are associated with hypogonadism, most likely acting via the leptin pathway.

There are no known human mutations of the GnRH gene, but several families with mutations in the GnRH receptor have been described. These mutations account for 2-14% of idiopathic HH without anosmia. The severity of the defect is variable and many patients will respond to high-dose GnRH with increased gonadotropin secretion, indicating that the receptor defect is partial and not complete.

Mutations in gonadotropin genes are extremely rare. Mutations in the common α-subunit are not known in humans. Mutations in the LH-β subunit have been described in a few individuals and may lead to low, absent, or elevated LH levels, depending on the mutation. Defects in the FSH-β subunit may be the cause of azoospermia in a few rare cases.

Children with X-linked congenital adrenal hypoplasia have associated HH as a result of impaired GnRH secretion. In these patients, there is a mutation of the DAX1 gene at Xp21.2-21.3. Conditions occasionally associated with these patients because of the contiguous gene syndrome include glycerol kinase deficiency, Duchenne muscular dystrophy, and ornithine transcarbamoyltransferase deficiency. Most boys with DAX1 mutations develop HH in adolescence, although a patient with adult-onset adrenal insufficiency and partial HH and 2 females with HH and delayed puberty also have been described, the latter as part of extended families with males with classic HH. The DAX1 gene defect is, however, rare in patients with delayed puberty or HH without at least a family history of adrenal failure (see Chapter 576).

It should be noted that genotype–phenotype correlations in IHH appear to be complex and pedigrees with digenic or oligogenic inheritance have been described. The same genetic defect may be associated with Kallmann syndrome, normosmic IHH, additional birth defects, delayed normal puberty, or an apparently normal phenotype. This variability has been observed more frequently in kindreds with mutations in FGFR8/FGFR1 and in PROK2/PROKR2 ligand-receptor pairs, and may be from other interacting genes, epigenetic effects, or environmental factors.

**Other Disorders with Hypogonadotropic Hypogonadism**

HH has been observed in a few patients with polyglandular autoimmune syndrome, in some with elevated melatonin levels, and in those with a variety of other syndromes such as Bardet-Biedl, Prader-Willi, multiple lentigines, and several ataxia syndromes. In rare cases, HH is associated with complex chromosomal abnormalities.

**Hypogonadotropic Hypogonadism Associated with Other Pituitary Hormone Deficiencies**

Defects in pituitary transcription factors such as PROP-1, HESX-1, LHX-4, SOX-3, and LHX-3 lead to multiple pituitary deficiencies, including HH. Most of these present with multiple pituitary hormone deficiency in infancy, but some cases (especially with PROP-1 mutations) may present with hypogonadism or hypoadrenalism in adult life. Growth hormone is almost always affected in multiple pituitary hormone deficiency, but thyroid-stimulating hormone and adrenocorticotropic hormone may be spared in some cases. In patients with organic lesions in or near the pituitary, the gonadotropin deficiency is usually pituitary in origin. Microphallus (<2.5 cm at term) in the newborn male with growth hormone deficiency suggests the possibility of gonadotropin deficiency.

**DIAGNOSIS**

Levels of gonadotropins and gonadal steroids are elevated for up to 6 mo after birth (minipuberty), and if the diagnosis of HH is suspected in early infancy these levels will be found to be inappropriately low. By the second half of the 1st yr of life these levels normally decline to near zero and remain suppressed until late childhood. Therefore, routine lab tests cannot distinguish HH from normal suppression of gonadotropins in this age group. At the normal age of puberty, these patients fail to show clinical signs of puberty or normal increase in LH and FSH levels. Children with constitutional delay of growth and puberty will have the same clinical picture and similar lab findings (and these cases are far more common than true HH, especially in males), and their differentiation from patients with HH is extremely difficult. Dynamic testing with GnRH or hCG may not be able to distinguish these groups in a reliable manner. A testosterone level greater than 50 ng/dL (1.7 nmol/L) generally indicates that normal puberty is likely, but a lower level does not reliably distinguish these groups. At least 1 study shows that an inhibin B level of <35 pg/mL in Tanner stage 1 and <65 pg/mL in Tanner stage 2 may be able to distinguish IHH from constitutional delay in males.

Insulin-like growth factor-1, thyroid-stimulating hormone, free thyroxine, and morning cortisol levels should be checked to assess the status of other anterior pituitary hormones; dynamic testing for growth hormone deficiency and adrenal insufficiency may be necessary if these are abnormal or equivocal. HH is very likely if the patient has evidence of another pituitary deficiency, such as a deficiency of growth hormone, particularly if it is associated with adrenocorticotropic hormone deficiency. Hyperprolactinemia is a known cause of delayed puberty and should be excluded by determination of serum prolactin levels in all patients. The presence of anosmia usually indicates permanent gonadotropin deficiency, but occasional instances of markedly delayed puberty (18-20 yr of age) have been observed in anosmic individuals. Although anosmia may be present in the family or in the patient from early childhood, its existence is rarely volunteered, and direct questioning is necessary in all patients with delayed puberty. Formal olfactometry, such as the University of Pennsylvania Smell Identification Test, is advisable to determine if partial degrees of hyposmia are present because IHH patients display a broad spectrum of olfactory function.

In the absence of family history, it may not be possible to make the diagnosis of HH with certainty, but the diagnosis will become more and more likely as puberty is delayed further beyond the normal age. If pubertal delay persists beyond age 18 yr with low 8 am testosterone levels and inappropriately low gonadotropins (normal values are inappropriately low in this setting), then the patient can be presumptively diagnosed with HH. An MRI of the brain is indicated to look for
tumors and other anomalies in the hypothalamic-pituitary region. Genetic testing for pituitary transcription factors and several of the genes involved in isolated HH is also available and should be performed when possible. A renal ultrasound is recommended in patients with Kallmann syndrome because of its association with unilateral renal agenesis. Some authorities also recommend obtaining a baseline bone-density evaluation.

**Treatment**

**Constitutional delay of puberty** should be ruled out before a diagnosis of HH is established and treatment is initiated. Testicular volume of less than 4 mL by 14 yr of age occurs in approximately 3% of boys, but true HH is a rare condition. Even relatively moderate delays in sexual development and growth may result in significant psychologic distress and require attention. Initially, an explanation of the variations characteristic of puberty and reassurance suffice for the majority of boys. If by 15 yr of age no clinical evidence of puberty is beginning and the testosterone level is <50 ng/dL, a brief course of testosterone may be recommended. Various regimens are used, including testosterone enanthate 100 mg intramuscularly once monthly for 4-6 mo or 150 mg once monthly for 3 mo. Some practitioners use oral oxandrolone, which may have the theoretical advantage that it is not aromatized and may have less effect on bone age advancement (though definitive evidence of advantage is lacking). Oral oxandrolone may cause hepatic dysfunction and liver function tests should be monitored if it is used. Treatment is not necessary in all cases of constitutional delay, but if used, it is usually followed by normal progression through puberty and this may differentiate constitutional delay in puberty from isolated gonadotropin deficiency. The age of initiation of this treatment must be individualized.

Once a diagnosis of HH is made, treatment with testosterone will induce secondary sexual characteristics but will not stimulate testicular growth or spermatogenesis. Treatment with gonadotropins (either as a combination of hCG and human menopausal gonadotropins or using GnRH pulse therapy) will lead to testicular development, including spermatogenesis, but is much more complex to manage, so in most cases testosterone treatment is the best option. Either long-acting testosterone injections or daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are infrequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly every 3-4 wk, with 50 mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older boys, larger initial doses and increments can achieve more rapid virilization.

Treatment with gonadotropins is more physiologic but is expensive and complex, so it is less commonly used in adolescence. This treatment may be attempted in adult life when fertility is desired. The treatment schedule varies from 1,250-5,000 IU hCG in combination with 12.5-150 IU human menopausal gonadotropins 3 times per wk intramuscularly. It may require up to 2 yr of treatment to achieve adequate spermatogenesis in adults. Recombinant produced gonadotropins (LH and FSH) are also able to stimulate gonadal growth and function but are much more expensive. Treatment with GnRH (when available) is the most physiologically appropriate, but it requires the use of a subcutaneous infusion pump to deliver appropriately pulsed therapy because continuous exposure to GnRH will suppress gonadotropins rather than stimulate them. In some cases, patients with GnRH defects also have pituitary or testicular dysfunction (a “dual defect”) and may fail to respond adequately to GnRH or gonadotropin treatment. The rare patient with isolated LH deficiency can be treated effectively using hCG injections.

It has been found that up to 10% of patients diagnosed with HH (with or without anosmia) may exhibit spontaneous reversal of hypo-gonadism with sustained normal gonadal function when treatment has been discontinued; this may occur in patients with known genetic mutations in various genes, including FGFR1, PROK2, GNRH, CHD7, and TAC/TACR3. Such recovery is more likely in patients who show an increase in testicular volume during treatment or when treatment has been discontinued. Therefore, a brief trial of interruption of treatment is justified in patients with idiopathic HH. However, the recovery of gonadal function may not be lifelong.

*Bibliography is available at Expert Consult.*
Bibliography
Pseudoprecocity Resulting from Tumors of the Testes

Omar Ali and Patricia A. Donohoue

Leydig cell tumors of the testes are rare causes of precocious pseudo-puberty (gonadotropin-independent) and cause asymmetric enlargement of the testes. Leydig cells are sparse before puberty and tumors derived from them are more common in the adult, but rare cases do occur in children and the youngest reported case was in a 1 yr old boy. Although up to 10% of adult tumors may be malignant, metastasizing malignant tumors have not been reported in children, and pediatric Leydig cell tumors are usually unilateral and benign. Some tumors may be due to somatic activating mutations of the luteinizing hormone receptor.

The clinical manifestations are those of puberty in the male; onset usually occurs at 5-9 yr of age. Gynecomastia has been described. The tumor of the testis can usually be readily felt; the contralateral unaffected testis is normal in size for the age of the patient.

Plasma levels of testosterone are markedly elevated, and follicle-stimulating hormone and luteinizing hormone levels are suppressed. Ultrasonography may aid in the detection of small nonpalpable tumors. Fine-needle aspiration biopsy may help define the diagnosis.

Treatment consists of surgical removal of the affected testis. These tumors are generally resistant to chemotherapy. Progression of virilization ceases after removal of the tumor, and partial reversal of the signs of precocity may occur.

Testicular adrenal rests may develop into tumors that mimic Leydig cell tumors. Adrenal rest tumors are usually bilateral and occur in children with inadequately controlled congenital adrenal hyperplasia, usually of the salt-losing variety, during adolescence or young adult life. The stimulus for the growth of the adrenal rests is inadequate corticosteroid suppressive therapy causing excess adrenocorticotropic hormone secretion, and treatment with adequate doses almost always results in their regression. These tumors are histologically similar to primary Leydig cell tumors, but definitive evidence of the origin of these may be achieved by demonstrating their 21-hydroxylase activity. Misdiagnosis of these tumors as primary Leydig cell tumors may lead to unnecessary orchidectomy and should be avoided.

Fragile X syndrome (see Chapter 81.5) is caused by the amplification of a polymorphic CGG repeat in the 5′ untranslated region of the FMRI gene at Xp17.3. The gene encodes an RNA binding protein that is highly expressed in the brain and the testis. In otherwise normal individuals, 6-50 CGG repeats are present in the gene; the presence of 50-200 repeats (permutation) is associated with mild intellectual disability and other abnormalities, and the presence of more than 200 repeats (fragile X mutation) is associated with the classic fragile X syndrome. Permutations are present in 1 in 1,000 white males, and
mutations are found in 1 in 4,000-8,000. A cardinal characteristic of the condition is testicular enlargement (macroorchidism), reaching 40-50 mL after puberty. Although the condition has been recognized in a child as young as 5 mo of age, affected boys younger than 6 yr of age rarely have testicular enlargement; by 8-10 yr of age, most have testicular volumes greater than 3 mL. The testes are enlarged bilaterally, are not nodular, and are histologically normal. Results of hormonal studies are normal. Direct DNA analysis searching for CGG repeat sequences permits definitive diagnosis.

Large-cell calcifying Sertoli cell tumors of the testes and sex cord tumors with annular tubules are extremely rare Sertoli cell tumors that may be a cause of breast development in young boys. These tumors are usually associated with Peutz-Jeghers syndrome or Carney complex; they often occur bilaterally, are multifocal, and are detectible by ultrasonography. Excessive production of aromatase (P450arom), the enzyme that converts testosterone to estradiol, causes feminization of these boys. Because they are usually benign, they may be left in place if they are not causing pain; the gynecomastia can be treated with aromatase inhibitors.

In boys with unilateral cryptorchidism, the contralateral testis is approximately 25% larger than normal for age. Testicular enlargement has also been noted in boys with Henoch-Schönlein purpura and lymphangiectasia. Epidermoid and dermoid cysts of the testes have been reported rarely.

Bibliography is available at Expert Consult.
Bibliography
Gynecomastia, the proliferation of mammary glandular tissue in the male, is a common condition. True gynecomastia (the presence of glandular breast tissue) needs to be distinguished from pseudogynecomastia, which is the result of accumulation of adipose tissue in the area of the breast that is commonly seen in overweight boys. True gynecomastia is characterized by the presence of a palpable fibroglandular mass at least 0.5 cm in diameter, located concentrically beneath the nipple and areolar region.

**PHYSIOLOGIC FORMS OF GYNECOMASTIA**

Gynecomastia occurs in many newborn males as a result of normal stimulation by maternal estrogen; the effect usually disappears in a few weeks. It is then extremely rare in prepubertal boys, in whom it should always be investigated to identify the cause, but again becomes common during normal puberty.

**Neonatal Gynecomastia**

Transient gynecomastia occurs in 60-90% of male newborns secondary to exposure to estrogens during pregnancy. Breast development may be asymmetrical and galactorrhea is seen in approximately 5%. Most cases resolve within 4-8 wk of birth, but a few can last as long as 12 mo.

**Pubertal Gynecomastia**

During early puberty to midpuberty, up to 70% of boys develop various degrees of subareolar hyperplasia of the breasts. Incidence peaks at 14 yr of age, at Tanner stage 3-4 and at a testicular volume of 5-10 mL. Physiologic pubertal gynecomastia may involve only 1 breast; it is not unusual for both breasts to enlarge at disproportionate rates or at different times. Tenderness of the breast is common but transitory. Spontaneous regression may occur within a few months; it rarely persists longer than 2 yr. Significant psychosocial distress may be present, especially in obese boys with relatively large breasts.

The cause is thought to be an imbalance between estrogen and androgen action at the level of breast tissue. Testing usually fails to reveal any significant difference in circulating estrogen and androgen levels between affected and unaffected males, but minor degrees of imbalance in free hormone levels may still be present. Other hormones, including leptin and luteinizing hormone, may directly stimulate breast development and may play a role in pubertal gynecomastia. Some cases may be caused by an increased sensitivity to estrogens and/or relative androgen resistance in the affected tissue. As androgen levels continue to rise in later puberty, most cases resolve.

**Pathologic Gynecomastia**

See Table 585-1.

**Monogenic forms of gynecomastia** are extremely rare, but do exist. Familial gynecomastia has occurred in several kindreds as an X-linked or autosomal dominant sex-limited trait. Some of these cases were found to be caused by constitutive activation of the P450 aromatase enzyme (CYP19A1 gene), leading to increased peripheral conversion of C-19 steroids to estrogens (increased aromatization). A report of this syndrome in a father and his son and daughter suggests autosomal dominant inheritance. Excess aromatase activity was shown in skin fibroblasts and transformed lymphocytes in vitro.

**Exogenous sources of estrogens** are an important cause of gynecomastia in prepubertal children. Very small amounts of estrogens can cause gynecomastia in male children and accidental exposure may occur by inhalation, percutaneous absorption, or ingestion. Common sources of estrogens include oral contraceptive pills and oral and transdermal estrogen preparations. Gynecomastia has been reported in workers involved in the manufacture of estrogens and even in the children of such workers. Gynecomastia can also occur secondary to exposure to medications that decrease the level of androgens (especially free androgens), increase estradiol, or displace androgens from breast androgen receptors. Spironolactone, alkylating agents, anabolic steroids, human chorionic gonadotropin, ketoconazole, cimetidine, and androgen inhibitors such as flutamide are all associated with the occurrence of gynecomastia. Weaker associations are seen with a large number of other medications and drugs of abuse, including opiates, alcohol, and marijuana, although the association with marijuana may not be as strong as previously thought. Lavender, tea oils, and excessive consumption of soy are also implicated as causes of prepubertal gynecomastia.

**Klinefelter syndrome** and other causes of male hypogonadism are strongly associated with gynecomastia. Significant gynecomastia is seen in 50% of adolescents with Klinefelter syndrome; it is also seen in other conditions characterized by male undervirilization, including partial androgen insensitivity syndrome and 17-ketosteroid reductase deficiency. Gynecomastia has also been observed in children with congenital virilizing adrenal hyperplasia (11β-hydroxylase deficiency) and with Leydig cell tumors of the testis or with feminizing tumors of the adrenal gland. Several boys with Peutz-Jeghers syndrome and gynecomastia had sex cord tumors of the testes. The testes may not be enlarged in these cases and the tumor is usually multifocal and bilateral. Excessive aromatase production accounts for the gynecomastia. When gynecomastia is associated with galactorrhea, a prolactinoma should be considered. Hyperthyroidism alters the androgen to estrogen ratio by increasing bound androgen and decreasing the free testosterone and may result in gynecomastia in up to 40% of cases. Gynecomastia is also seen in malnourished patients after restoration of normal nutrition (refeeding syndrome), in whom it may be from hepatic dysfunction or abnormal activation of the gonadotropin axis.

**Evaluation of Gynecomastia**

In pubertal cases a detailed history and physical examination may be all that is needed to exclude rare pathologic causes. Historical evaluation should include family history of male relatives with gynecomastia, history of liver or renal disease, use of medications or drugs of abuse, and exposure to herbal and cosmetic products that may contain phytoestrogens. Physical examination should include special attention to the breasts (looking for overlying skin changes, fixation, local lymphadenopathy, and nipple discharge) as well as a testicular exam. No
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<td>Decreased energy, vitality</td>
<td>Mild normocytic, normochromic anemia (normal female range)</td>
</tr>
<tr>
<td>Decreased motivation, self-confidence</td>
<td>Depressed mood, mild depression or dysthymia</td>
</tr>
<tr>
<td>Feeling sad or blue, irritability</td>
<td>Reduced muscle bulk and strength</td>
</tr>
<tr>
<td>Weakness, decreased physical or work performance</td>
<td>Increased body fat or body mass index</td>
</tr>
<tr>
<td>Poor concentration and memory</td>
<td>Fine facial skin wrinkling (lateral to orbits and mouth)</td>
</tr>
<tr>
<td>Increased sleepiness</td>
<td></td>
</tr>
</tbody>
</table>


Laboratory evaluation is indicated in routine cases with no other associated abnormality but all prepubertal cases, as well as pubertal cases with suspicious features, should be investigated; initial laboratory evaluation should include thyroid function tests (to rule out hyperthyroidism), testosterone, estradiol, human chorionic gonadotropin, luteinizing hormone, and prolactin levels. Most cases of hyperprolactinemia are associated with galactorrhea, but there are a few reports of hyperprolactinemia causing gynecomastia without associated galactorrhea. Because of circadian variation, these levels should ideally be obtained in the morning. Other tests that may be indicated in selected cases include a karyotype, dehydroepiandrosterone sulfate, and liver and renal function tests. Gonadotropin levels may be a useful screen for Klinefelter syndrome and will be elevated in pubertal boys with this condition. If elevated, a karyotype should be performed.

**TREATMENT**

Treatment in case of benign pubertal gynecomastia usually consists of reassuring the boy and his family of the physiologic and transient nature of the phenomenon. When the enlargement is striking and persistent and causes serious emotional disturbance to the patient, specific treatment may be justified. Unfortunately, medical treatment is generally ineffective in long-standing cases. Early cases respond better to medical treatment but it is harder to justify treatment as most cases will resolve spontaneously. Agents that have been used for medical treatment include androgens, aromatase inhibitors, and estrogen antagonists. The effectiveness of synthetic androgens is variable and side effects are a concern, so these are rarely used in pediatrics. Aromatase inhibitors make physiologic sense, but placebo-controlled trials have been disappointing. Estrogen antagonists like tamoxifen and raloxifene are more effective, with raloxifene being the superior agent in at least 1 well-designed trial. If medical treatment is attempted, it should be in early cases (<12 mo standing) using raloxifene (in a dose of 60 mg/day) or tamoxifen (10-20 mg/day) for 3-9 mo, with the understanding that success rates are generally low in severe cases and mild cases will likely resolve on their own without treatment.

In those cases where breast development is excessive (Tanner stages 3-5), causes significant psychologic distress, and fails to regress in 18-24 mo, surgical removal of the enlarged breast tissue may be indicated, particularly in boys who have completed or nearly completed pubertal development. Careful examination and laboratory testing to exclude nonphysiologic causes are advisable before proceeding to surgery.

_Bibliography is available at Expert Consult._
Bibliography


Hypofunction of the ovaries can be either primary or central in etiology. It may be caused by congenital failure of development, postnatal destruction (primary or hypergonadotropic hypogonadism), or lack of central stimulation by the pituitary and/or hypothalamus (secondary or tertiary hypogonadotropic hypogonadism). **Primary ovarian insufficiency** (hypergonadotropic hypogonadism), which is also termed **premature ovarian failure**, is characterized by the arrest of normal ovarian function before the age of 40 yr. Certain genetic mutations can result in primary ovarian insufficiency. Hypofunction of the ovaries because of a lack of central stimulation (hypogonadotropic hypogonadism) can be associated with other processes, such as multiple pituitary hormone deficiencies and some chronic diseases. Table **586-1** details the etiologic classification of ovarian hypofunction.

**586.1 Hypergonadotropic Hypogonadism in the Female (Primary Hypogonadism)**

*Alvina R. Kansra and Patricia A. Donohoue*

Diagnosis of hypergonadotropic hypogonadism before puberty is difficult. Except in the case of Turner syndrome, most affected patients have no prepubertal clinical manifestations.
HYPOGONADOTROPIC HYPOGONADISM

**Etiologic Classification of Ovarian Hypofunction**

<table>
<thead>
<tr>
<th>HYPOGONADOTROPIC HYPOGONADISM</th>
<th>Etiologic Classification of Ovarian Hypofunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothalamic</strong></td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Kallmann syndrome (KAL1, FGF1, FGF8, PROKR2, CHD7, WDR11, NELF, SEMA3A)</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Other gene defects: leptin, leptin receptor, KISS-1 (deficiency of kisspeptin), DAX-1, TAC3 (deficiency of neurokinin B), TACR3, SEMA7A</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Inherited syndromes: Prader-Willi, Bardet-Biedl, and others</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Marked constitutional growth delay</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>Acquired defects (reversible)</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Anorexia nervosa</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Drug use</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Malnutrition</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Chronic illness, especially Crohn disease</td>
<td>Genetic defects</td>
</tr>
<tr>
<td>• Hyperprolactinemia</td>
<td>Genetic defects</td>
</tr>
</tbody>
</table>

**Pituitary**

Genetic defects

- Isolated gonadotropin deficiency (GnRH receptor, FSH, and LH β-subunit)
- Septooptic dysplasia (HESX-1 in some cases)
- Disorders of pituitary organogenesis (PROP1, LH23, LH4X, SOX-3, etc.)
- Acquired defects
- Pituitary tumors
- Pituitary infarction
- Infritative disorders (histiocytosis, sarcoidosis)
- Hemosiderosis and hemochromatosis
- Radiation

**HYPERGONADOTROPIC HYPOGONADISM**

Genetic

Follicle-stimulating hormone and luteinizing hormone resistance

Mutations in sterioiodogenic pathways

46,XX gonadal dysgenesis

Turner syndrome and its variants

Noonan syndrome (PTPN11 gene)

SF-1 gene mutations

Galactosemia

Fragile X-associated disorders

Bloom syndrome

Werner syndrome

Ataxia-telangiectasia

Fanconi anemia

**Acquired**

Chemotherapy

Radiation

Autoimmune ovarian failure from autoimmune polyendocrine syndromes 1 and 2

**TURNER SYNDROME**

**Clinical Manifestations**

Many patients with Turner syndrome are recognizable at birth because of a characteristic edema of the dorsa of the hands and feet and loose skinfolds at the nape of the neck. Low birthweight and decreased birth length are common (see Chapter 81). Clinical manifestations in childhood include webbing of the neck, a low posterior hairline, small mandible, prominent ears, epicanthal folds, high arched palate, a broad chest presenting the illusion of widely spaced nipples, cubitus valgus, and hyperconvex fingernails. The diagnosis is often first suspected at puberty when breast development fails to occur.

**Short stature**, the cardinal finding in virtually all girls with Turner syndrome, may be present with little in the way of other clinical manifestations. The linear growth deceleration begins in infancy and young childhood, gets progressively more pronounced in later childhood and adolescence, and results in significant adult short stature. Sexual maturation (breast development) fails to occur at the expected age; however, signs of adrenarche (pubic hair) are normally present. Among untreated patients with Turner syndrome, the mean adult height is 143.1-144 cm in the United States and most of northern Europe, but 140 cm in Argentina and 147 cm in Scandinavia (Fig. 586-1). The height is well correlated with the midparental height (average of the parents’ heights). Specific growth curves for height have been developed for girls with Turner syndrome.

Associated cardiac defects are common. In the girls with Turner syndrome, life-threatening consequences of X-chromosome haploinsufficiency involve the cardiovascular system. There is a 4-5-fold increased rate of premature mortality secondary to congenital heart disease and premature coronary heart disease in adults with Turner syndrome. Clinically silent cardiac defects, mainly bicuspid aortic valve but also ascending aortic dilation, coarctation of the aorta, and partial anomalous pulmonary venous connections, are present in patients with Turner syndrome. Regardless of the age, all patients with Turner syndrome at the time of diagnosis need comprehensive cardiovascular evaluation by a cardiologist specializing in congenital heart disease. Complete cardiologic evaluation, including echocardiography, reveals isolated nonstenotic bicuspid aortic valves in one third to one half of patients. In later life, bicuspid aortic valve disease can progress to dilation of the aortic root. Less-frequent defects include aortic coarctation (20%), aortic stenosis, mitral valve prolapse, and anomalous pulmonary venous drainage. In 1 study, 38% of patients with 45, X chromosomes had cardiovascular malformations compared with 11%
of those with mosaic monosomy X, the most common were aortic valve abnormalities and aortic coarctation. Webbed neck in patients with or without recognized chromosome syndromes is associated with both flow-related and non–flow-related heart defects. Among patients with Turner syndrome, those with webbed necks have a much greater chance of having coarctation of the aorta than do those without webbed necks. Transthoracic echocardiogram in young girls is adequate if cardiac anatomy is clearly seen; otherwise magnetic resonance angiographic screening studies should be considered even in asymptomatic individuals with Turner syndrome. During adolescence, and certainly before pregnancy (when possible) is contemplated, repeat cardiac evaluation should be considered even in those without prior findings of cardiac abnormalities. Blood pressure should be routinely monitored even in the absence of cardiac or renal lesions and especially in those with suggestions of aortic root dilation. Cardiac MRI is a valuable tool to detect and monitor aortic root dilation.

Renal ultrasound should be performed in all girls with Turner syndrome at diagnosis. One fourth to one third of patients have renal malformations on ultrasonographic examination (50% of those with 45,X karyotypes). The more serious defects include pelvic kidney, horseshoe kidney, double collecting system, complete absence of 1 kidney, and ureteropelvic junction obstruction. Some of the malformations may increase the risk of hypertension and urinary tract infection. Idiopathic hypertension is also common. Girls with Turner syndrome who had normal baseline renal ultrasound findings did not develop renal disease during a follow-up period averaging 6 yr.

When the ovaries were examined by ultrasonography, older studies found a significant decrease in percentage of detectable ovaries from infancy to later childhood. A subsequent report found no such age-related differences in a cross-sectional and longitudinal study; 27–46% of patients had detectable ovaries at various ages; 76% of those with X mosaicism and 26% of those with 45,X karyotypes had detectable ovaries.

Sexual maturation usually fails to occur, but 10–20% of girls have spontaneous breast development, and a small percentage may have menstrual periods. Primary gonadal failure is associated with early onset of adrenal hyperplasia (elevation in dehydroepiandrosterone sulfate) but delayed pubarche (pubic hair development). Spontaneous pregnancies have been reported in menstruating patients with Turner syndrome. Premature menopause, increased risk of miscarriage, and offspring with increased risk of trisomy 21 have been reported. A woman with a 45,X/46,X,r(X) karyotype treated with hormone replacement therapy had 3 pregnancies, resulting in a normal 46,XY male infant, a spontaneous abortion, and a healthy term female with Turner syndrome 45,X/46,Xr(X).

Antithyroid antibodies (thyroid peroxidase, and/or thyroglobulin antibodies) occur in 30–50% of patients. The prevalence increases with advancing age. Autoimmune thyroid disease, with or without the presence of a goiter, occurs in 10–30% of patients. Age-dependent abnormalities in carbohydrate metabolism characterized by abnormal glucose tolerance and insulin resistance and, only rarely, frank type 2 diabetes occur in older patients with Turner syndrome. Impaired insulin secretion has been described in 45,X women. Cholesterol levels are elevated in adolescence, regardless of body mass index or karyotype.

Inflammatory bowel disease, both Crohn disease and ulcerative colitis, gastrointestinal bleeding because of abnormal mesenteric vascularity, and delayed gastric emptying time have all been reported. Screening for celiac disease is recommended by recent guidelines, as the risk of celiac disease is increased in Turner syndrome, with 4–6% of individuals affected. Although autoimmune diseases have been associated with Turner syndrome, the prevalence of type 1 diabetes with Turner syndrome is not very high.

Sternal malformations can be detected by lateral chest radiography. An increased carrying angle at the elbow is usually not clinically significant. Scoliosis occurs in approximately 10% of adolescent girls. Congenital hip dysplasia occurs more commonly than in the general population. Reported eye findings include anterior segment dysgenesis and keratoconus. Pigmented nevi become more prominent with age; melanocytic nevi are common. Essential hyperhidrosis, torus mandibularis, and alopecia areata occur rarely.

Recurrent bilateral otitis media develops in approximately 75% of patients. Sensorineural hearing deficits are common, and the frequency increases with age. Problems with gross and fine motor-sensory integration, failure to walk before 15 mo of age, and early language dysfunction often raise questions about developmental delay, but intelligence is normal in most patients. However, cognitive impairment does occur in patients with 45,X/46,X,r(X); the ring chromosome is unable to undergo inactivation and leads to 2 functional X chromosomes.

Special attention should be given to psychosocial development in girls with Turner syndrome. In general, the behavior function is normal in girls with Turner syndrome, but they are at an increased risk for social isolation, immaturity, and anxiety. Other conditions, such as dyslexia, nonverbal learning disability, and attention deficit disorder, have been reported in girls with Turner syndrome. In adults, deficits in perceptual spatial skills are more common than they are in the general population. Some unconfirmed data suggest the existence of an imprinted X-linked locus that affects cognitive function such as verbal and higher-order executive function skills. These functions are apparently better when the X is paternal in origin.

The prevalence of mosaicism depends in large part on the techniques used for studying chromosomal patterns. The use of fluorescent in situ hybridization and reverse transcription–polymerase chain reaction (PCR) has increased the reported prevalence of mosaic patterns to as high as 60–74%.

Mosaicism involving the Y chromosome occurs in 5%. A population study using PCR with 5 different primer sets found Y chromosome material in 12.2%. Gonadoblastoma among Y-positive patients occurred in 7–10%. Therefore, the recommendation is that prophylactic gonadectomy should be performed even in the absence of MRI or CT evidence of tumors. The recommended timing of this procedure is...
at the time of diagnosis, but this may need to be reevaluated in the future. The gonadoblastoma locus on the Y chromosome (GBY) maps close to the Y centromere. The presence of only the SRY (sex-determining region on the Y chromosome) locus is not sufficient to confer increased susceptibility for the development of gonadoblastoma. A detailed study of 53 patients with Turner syndrome by nested PCR excluded low-level Y mosaicism in almost all cases. A second round of PCR detected SRY on the distal short arm of the Y chromosome in only 2 subjects. Therefore, routine PCR for Y chromosome detection for the purpose of assigning gonadoblastoma risk is not indicated. High-throughput quantitative genotyping may provide an effective and inexpensive method for the identification of X chromosome abnormalities and Y chromosome material identification.

In patients with 45,X/46,XX mosaicism, the clinical abnormalities are attenuated and fewer; short stature is as frequent as it is in the 45,X patient and may be the only manifestation of the condition other than ovarian failure (see Fig. 586-1).

**Laboratory Findings**

Chromosomal analysis must be considered routinely in short girls. In a systematic search, using Southern blot analysis of leukocyte DNA, Turner syndrome was detected in 4.8% of girls referred to an endocrinology service because of short stature. Patients with a marker chromosome in some or all cells should be tested for DNA sequences at or near the centromere of the Y chromosome for GBY.

Ultrasoundography of the heart, kidneys, and ovaries is indicated after the diagnosis is established. The most common skeletal abnormalities are shortening of the 4th metatarsal and metacarpal bones, epiphyseal dysgenesis in the joints of the knees and elbows, Madelung deformity, scoliosis, and in older patients, inadequate osseous mineralization.

Plasma levels of gonadotropins, particularly follicle-stimulating hormone (FSH), are markedly elevated to greater than those of age-matched controls during infancy; at 2-3 yr of age, a progressive decrease in levels occurs until they reach a nadir at 6-8 yr of age, and by 10-11 yr of age, they rise to adult castrate levels.

Antithyroid peroxidase and antithyroglobulin antibodies should be checked periodically, and if positive, levels of thyroxine and thyroid-stimulating hormone should be obtained. Turner syndrome girls should be screened for **celiac disease** by measuring tissue transglutaminase immunoglobulin A antibodies. Initial testing should be done around age 4 yr and repeated every 2-5 yr. Extensive studies have failed to establish that growth hormone deficiency plays a primary role in the pathogenesis of the growth disorder. Defects in normal secretory patterns of growth hormone are seen in adolescents because of a lack of gonadal steroids, but not in younger girls with Turner syndrome. In vitro, monocytes and lymphocytes show decreased sensitivity to insulin-like growth factor 1.

**Treatment**

Treatment with recombinant human growth hormone increases height velocity and ultimate stature in most, but not all, children with Turner syndrome. Many girls achieve heights of greater than 150 cm with early initiation of treatment. In a large, multicenter, placebo-controlled clinical trial, 99 patients with Turner syndrome who started receiving growth hormone at a mean age of 10.9 yr at doses between 0.27 and 0.36 mg/kg/wk achieved a mean height of 149 cm, with nearly one third reaching heights greater than 152.4 cm (60 in). In the Netherlands, higher doses of growth hormone (up to 0.63 mg/kg/wk in the 3rd yr of treatment) resulted in 85% of the subjects reaching adult heights in the normal range for the Dutch reference population. Growth hormone treatment should be initiated in early childhood and/or when there is evidence of height velocity attenuation on specific Turner syndrome growth curves. The average starting dose of growth hormone is 0.375 mg/kg/wk. Growth hormone therapy does not significantly aggravate carbohydrate tolerance and does not result in marked adverse events in patients with Turner syndrome. Serum levels of insulin-like growth factor 1 should be monitored if the patient is receiving high doses of growth hormone. If the insulin-like growth factor 1 levels are significantly elevated, the dose of growth hormone may need to be reduced. Treatment with growth hormone can cause excessive growth of the hands and feet in some girls with Turner syndrome.

Oxandrolone has also been used to treat the short stature associated with Turner syndrome, either alone or in combination with growth hormone. This synthetic anabolic steroid has weak androgenic effects, and patients should be monitored for signs of pubarche, as well as hepatotoxicity. The latter is rare.

Replacement therapy with estrogens is indicated, but there is little consensus about the optimal age at which to initiate treatment. The psychologic preparedness of the patient to accept therapy must be taken into account. The improved growth achieved by girls treated with growth hormone in childhood permits initiation of estrogen replacement at 12-13 yr. Delaying estrogen therapy to optimize height potential until 15 yr of age, as previously recommended, seems unwarranted. This change to starting earlier estrogen therapy was considered because of the psychologic importance of age-appropriate pubertal maturation. Also, delaying estrogen therapy could be deleterious for bone health and other aspects of the child’s health. Low-dose estrogen replacement at 12 yr of age permits a normal pace of puberty without interfering with the positive effect of growth hormone on the final adult height. Estrogen therapy improves verbal and nonverbal memory in girls with Turner syndrome. In young women with age-appropriate pubertal development who achieve normal height, health-related quality-of-life questionnaires have yielded normal results.

Although many forms of estrogen are available, oral estrogens have been mostly used. Even though transdermal and injectable depot forms of estradiol may be alternative physiologic options, transdermal patches are increasing in popularity. This is because transdermal patches bypass the first hepatic metabolism, thereby requiring only a small amount of estrogen to attain the adequate levels for its function. For oral preparation a conjugated estrogen (Premarin), 0.15-0.625 mg daily, or micronized estradiol (Estrace), 0.5 mg given daily for 3-6 mo, is usually effective in inducing puberty. The recommendations for transdermal patch are 6.25 μg daily that is gradually increased over 2 yr to the adult dose of 100-200 μg daily. The estrogen then is cycled (taken on days 1-23) and a progesterin (Provera) is added (taken on days 10-23) in a dose of 5-10 mg daily. In the remainder of the calendar month, during which no treatment is given, withdrawal bleeding usually occurs.

Prenatal chromosome analysis for advanced maternal age has revealed a frequency of 45,X/46,XX that is 10 times higher when than diagnosed postnatally. Most of these patients have no clinical manifestations of Turner syndrome, and levels of gonadotropins are normal. Awareness of this mild phenotype is important in counseling patients.

Psychosocial support for these girls is an integral component of treatment. A comprehensive psychologic education evaluation is recommended either at the time of Turner syndrome diagnosis, depending on the patient’s age, when any of the components of behavior or cognition become obvious, or immediately preceding school entry. The Turner Syndrome Society, which has local chapters in the United States, and similar groups in Canada and other countries provide a valuable support system for these patients and their families in addition to that given by the healthcare team.

Successful pregnancies have been carried to term using ovum donation and in vitro fertilization. Adolescents with few signs of spontaneous puberty may have ovaries with follicles. There remains a future possibility of using cryopreserved ovarian tissue with immature oocytes before the regression of the ovaries for the future pregnancies. In adult women with Turner syndrome, there seems to be a high prevalence of undiagnosed bone mineral density, lipid, and thyroid abnormalities. Glucose intolerance, diminished 1st-phase insulin response, elevated blood pressure, and lowered fat-free mass are common. Glucose tolerance worsens, but fat-free mass and blood pressure and general physical fitness improve with sex hormone replacement. The neurocognitive profile of adult women is unaffected by estrogen status.

**XX GONADAL DYSGENESIS**

Some phenotypically and genetically normal females have gonadal lesions identical to those in 45,X patients but without somatic features.
of Turner syndrome; their condition is termed pure gonadal dysgenesis or pure ovarian dysgenesis.

The disorder is rarely recognized in prepubertal children because the external genitals are normal, no other abnormalities are visible, and growth is normal. At pubertal age, sexual maturation fails to take place. Plasma gonadotropin levels are elevated. Delay of epiphyseal fusion may result in a eunuchoid habitus. Pelvic ultrasonography reveals streak ovaries.

Affected siblings, parental consangunuity, and failure to uncover mosaicism all point to female-limited autosomal recessive inheritance. The disorder appears to be especially frequent in Finland (1 in 8,300 liveborn girls). In this population, several mutations in the FSH receptor gene (on chromosome 2p) were demonstrated as the cause of the condition. FSH receptor gene mutations were not detected in Mexican women with 46,XX gonadal dysgenesis. In some patients, XX gonadal dysgenesis has been associated with sensorineural deafness (Perrault syndrome). A patient with this condition and concomitant growth hormone deficiency and virilization has also been reported. There may be distinct genetic forms of this disorder. Müllerian agenesis, or the Mayer-Rokitansky-Küster-Hauser syndrome, which is second to gonadal dysgenesis as the most common cause of primary amenorrhea, occurring in 1 in 4,000-5,000 females, has been reported in association with 46,XX gonadal dysgenesis in a 17 yr old adolescent with primary amenorrhea and lack of breast development. One case of dysgerminoma with syncytiotrophoblastic giant cells was reported. An 18 yr old woman with primary amenorrhea and an absence of müllerian-derived structures, unilateral renal agenesis, and clinical signs of androgen excess, a phenotype resembling the Mayer-Rokitansky-Küster-Hauser syndrome, was found to have a loss-of-function mutation in the WNT4 gene. Treatment consists of estrogen replacement therapy.

45,X/46,XY GONADAL DYSGENESIS

45,X/46,XY gonadal dysgenesis, also called mixed gonadal dysgenesis, has extreme phenotypic variability postnatally that may extend from a Turner-like syndrome to a male phenotype with a penile urethra; it is possible to delineate 3 major clinical phenotypes. Short stature is a major finding in all affected children. Ninety percent of prenatally diagnosed cases have a normal male phenotype.

Some patients have no evidence of virilization; they have a female phenotype and often have the somatic signs of Turner syndrome. The condition is discovered prepubertally when chromosomal studies are made in short girls, or later when chromosomal studies are made because of failure of sexual maturation. Fallopian tubes and uterus are present. The gonads consist of intraabdominal undifferentiated streaks; chromosomal study of the streak often reveals an XY cell line. The streak gonad differs somewhat from that in girls with Turner syndrome, and a small proportion of affected girls are well coordinated, socially outgoing, and academically superior.

XXX, XXXX, AND XXXXX FEMALES

XXX Females

The 47,XXX (trisomy) chromosomal constitution is the most frequent extra-X chromosome abnormality in females, occurring in almost 1 in 1,000 liveborn females. In 68%, this condition is caused by maternal meiotic nondisjunction, but most 45,X and half of 47,XXX constitutions are caused by paternal sex chromosome errors. The phenotype is that of a normal female; affected infants and children are not recognized based on the genital appearance.

Sexual development and menarche are normal. Most pregnancies have resulted in normal infants. By 2 yr of age, delays in speech and language become evident and lack of coordination, poor academic performance, and immature behavior are seen in some. These girls tend to be tall and gangly, manifest behavior disorders, and are placed in special education classes. Using high-resolution MRI, 10 47,XXX subjects had lower amygdala volumes than 20 euploid controls; 10 47,XXX subjects had even lower amygdala volumes. In a review of 155 girls, 62% were physically normal. There is marked variability within the syndrome, and a small proportion of affected girls are well coordinated, socially outgoing, and academically superior.

XXXX and XXXXX Females

The great majority of females with these rare karyotypes have been intellectually challenged. Commonly associated defects are epicanthal folds, hypertelorism, clinodactyly, transverse palmar creases, radioulnar synostosis, and congenital heart disease. Sexual maturation is often incomplete and may not occur at all. Nevertheless, 3 women with the tetra-X syndrome gave birth, but no pregnancies were reported in 49,XXXXX women. Most 48,XXXX women tend to be tall, with an average height of 169 cm, whereas short stature is a common feature of the 49,XXXXX phenotype.

NOONAN SYNDROME

Girls with Noonan syndrome show certain anomalies that also occur in girls with 45,X Turner syndrome, but they have normal 46,XX chromosomes (see Chapter 81.4). The most common abnormalities are
the same as those described for males with Noonan syndrome (see Chapter 583.1). Short stature is one of the cardinal signs of this syndrome. The phenotype differs from Turner syndrome in several respects. Cognitive impairment is often present, the cardiac defect is most often pulmonary valvular stenosis or an atrial septal defect rather than an aortic defect, normal sexual maturation usually occurs but is delayed by 2 yr on average, and premature ovarian failure has been reported. Growth hormone therapy is approved by the FDA for use in Noonan syndrome patients with short stature.

**OTHER OVARIAN DEFECTS**

Some young women with no chromosomal abnormality are found to have streak gonads that may contain only occasional or no germ cells. Gonadotropins are increased. Cytotoxic drugs, especially alkylating agents such as cyclophosphamide and busulfan, procarbazine, etoposide, and exposure of the ovaries to irradiation for the treatment of malignancy are frequent causes of ovarian failure. Young women with Hodgkin disease demonstrate that combination chemotherapy and pelvic irradiation may be more deleterious than either therapy alone. Teenagers are more likely than older women to retain or recover ovarian function after irradiation or combined chemotherapy; normal pregnancies have occurred after such treatment. Treatment regimens may result in some ovarian damage in most girls treated for cancer. The median lethal dose for the human oocyte is estimated to be approximately 4 Gy; doses as low as 6 Gy have produced primary amenorrhea. Ovarian transposition before abdominal and pelvic irradiation in childhood can preserve ovarian function by decreasing the ovarian exposure to less than 4-7 Gy.

**Autoimmune ovarian failure** occurs in 60% of children older than 13 yr of age with type I autoimmune polyendocrinopathy (Addison disease, hypoparathyroidism, candidiasis). This condition, also known as *polyglandular autoimmune disease* type I is rare worldwide but not in Finland, where, as a result of a founder gene effect, it occurs in 1 in 25,000 people. The gene for this disorder is located on chromosome 21 and is associated with human leukocyte antigen (HLA) DR5. In patients with polyglandular autoimmune disease type I and ovarian failure, an association with HLA-A3 has been described. Affected girls may not develop sexually, or secondary amenorrhea may occur in young women. The ovaries may have lymphocytic infiltration or appear simply as streaks. Most affected patients have circulating steroid cell antibodies and autoantibodies to 21-hydroxylase. Among patients with polyglandular autoimmune syndromes, 5% were found to have hypogonadism.

The condition also occurs in young women as an isolated event or in association with other autoimmune disorders, leading to secondary amenorrhea (premature ovarian failure [POF]). It occurs in 0.2-0.9% of women younger than 40 yr of age. Premature ovarian failure is a heterogeneous disorder with many causes: chromosomal, genetic, enzymatic, infectious, and iatrogenic. When associated with autoimmune adrenal disease, steroid cell autoantibodies are always present. These antibodies react with P450csc, 17α-OH, or 21-OH enzymes. When associated with an entire host of endocrine and nonendocrine autoimmune diseases and not adrenal autoimmunity, steroid cell autoantibodies are rarely found. A second autoimmune disorder, often subclinical, is found in 10-39% of adult patients with POF. One 17 yr old with idiopathic thrombocytopenic purpura and 47,XXX chromosomes had autoimmune POF. Patients with POF do not have the neurocognitive defects found in Turner syndrome patients.

**Galactosemia**, particularly the classical form of the disease, usually results in ovarian damage, beginning during intrauterine life. Levels of FSH and luteinizing hormone (LH) are elevated early in life. Ovarian damage may be caused by deficient uridine diphosphate-galactose (see Chapter 58). The *Denys-Drash syndrome*, caused by a WTI mutation, can result in ovarian dysgenesis.

**Ataxia-telangiectasia** may be associated with ovarian hypoplasia and elevated gonadotropins; the cause is unknown. Gonadoblastomas and dysgerminomas have occurred in a few girls.

**Hypergonadotropic hypogonadism** has been postulated to also occur because of the resistance of the ovary to both endogenous and exogenous gonadotropins (Savage syndrome). This condition occurs also in women with POE. Antiovary antibodies or FSH receptor abnormalities may cause this condition. Mutation of the FSH receptor gene has been reported as an autosomal recessive condition (see Chapter 582). A few females with 46,XX chromosomes presenting in primary amenorrhea with elevated gonadotropin levels were found to have inactivating mutations of the LH receptor gene. This suggests that LH action is needed for normal follicular development and ovulation. Other genetic defects associated with ovarian failure include mutations in FOXL2, GNAS, CYP17, and CYP19. Some data also suggest that mutations within the gene encoding transcription factor SF-1 are associated with early ovarian failure.

Bibliography is available at Expert Consult.

### 586.2 Hypogonadotropic Hypogonadism in the Female (Secondary Hypogonadism)

**Alvina R. Kansra and Patricia A. Donohoue**

Hypogonadotropic hypogonadism is most commonly seen with multiple pituitary hormone deficiencies resulting from malformations (e.g., septooptic dysplasia, other midline defects), pituitary transcription factor defects such as in PROP-1, or lesions of the pituitary that are acquired postnatally. Familial isolated gonadotropin deficiency associated with anosmia (Kallmann syndrome) was described in 1944. Many other genetic causes for hypogonadotropic hypogonadism have been identified. A gene important in luteinizing hormone–releasing hormone secretion is named *KISS* (encoding the protein kisspeptin), which is suggested to play a significant role in the development of the luteinizing hormone–releasing hormone–secreting cells. Another set of genes recently implicated in hypogonadotropic hypogonadism are the genes for neurokinin B (*TAC3*) and its receptor (*TAC3R*).

In children with idiopathic hypopituitarism, the defect is usually found in the hypothalamus. In these patients, administration of gonadotropin-releasing hormone results in increased plasma levels of FSH and LH, establishing the integrity of the pituitary gland.

Hypogonadotropic hypogonadism is less common than hypergonadotropic hypogonadism. The latter condition, when associated with LH excess, underlies polycystic ovarian syndrome (Stein-Leventhal syndrome; see Chapter 552).

**Isolated Deficiency of Gonadotropins**

This heterogeneous group of disorders is characterized more fully with the use of the gonadotropin-releasing hormone analog stimulation test. In most children, the pituitary gland is normal, and the defect causing gonadotropin deficiency resides in the hypothalamus. Patients with hyperprolactinemia, most often caused by a pituitary prolactin-secreting adenoma, often have suppression of gonadotropin secretion. If breast development has occurred, then galactorrhea and amenorrhea are frequently seen.

Several sporadic instances of anosmia with hypogonadotropic hypogonadism have been reported. Anosmic hypogonadal females have
Bibliography


also been reported in kindreds with Kallmann syndrome, but hypogo-
nadism more frequently affects the males in these families. Mutations
in the gene for the \( \beta \)-subunit of FSH and LH have been reported.

Some autosomal recessive disorders, such as the Laurence-Moon-
Biedl, multiple lentigines, and Carpenter syndromes, appear in some
instances to include gonadotropic hormone deficiency. Patients with
Prader-Willi syndrome usually have some degree of hypogonadotropic
hypogonadism. Girls with severe thalassemia may have gonadotropin
deficiency from pituitary damage caused by chronic iron overload
secondary to multiple transfusions. Anorexia nervosa frequently
results in hypogonadotropic hypogonadism. The rare patients described
with leptin deficiency or leptin receptor defects have failure of pubertal
maturation because of gonadotropin deficiency.

**DIAGNOSIS**

The diagnosis may be apparent in patients with other deficiencies of
pituitary tropic hormones, but, as in males, it is difficult to differentiate
isolated hypogonadotropic hypogonadism from physiologic delay of
puberty. Repeated measurements of FSH and LH, particularly during
sleep, may reveal the rising levels that herald the onset of puberty.
Stimulation testing with gonadotropin-releasing hormone or one of its
analogs may help establish the diagnosis. Morbidity for both men and
women with hypogonadism includes infertility and an increased risk
of osteoporosis.

*Bibliography is available at Expert Consult.*
Bibliography
Girls with signs of early puberty may, in rare circumstances, have a lesion of the ovary as the etiology. These include tumors or cysts that secrete estrogenic, androgenic, or both types of hormones. In these patients the sex steroid production is not mediated by pituitary gonadotropin secretion, and thus they are said to produce pseudoprecocity.

Ovarian tumors are rare in the pediatric population, occurring at a rate of less than 3 in 100,000. Most ovarian masses are benign, but 10-30% may be malignant. If they occur before 8 yr of age they may cause signs of puberty. Ovarian malignancies, the most common genital neoplasms in adolescence, account for only 1% of childhood cancers. More than 60% are germ cell tumors, most of which are dysgerminomas that can secrete tumor markers as well as sex hormones (see Chapter 503). Five to 10% of germ cell tumors occur in phenotypic females with abnormal gonads associated with the presence of a Y chromosome. Next most common are epithelial cell tumors (20%), and nearly 10% are sex cord/stromal tumors (granulosa, Sertoli cell, and mesenchymal tumors). Multiple tumor markers can be seen in ovarian tumors, including α-fetoprotein, human chorionic gonadotropin, carcinoembryonic antigen, oncoproteins, p105, p53, KRAS mutations, cyclin D1, epidermal growth factor–related proteins and receptors, cathepsin B, and others. Variable levels of inhibin--activin subunit gene expression have been detected in ovarian tumors.

Functioning lesions of the ovary consist of benign cysts or malignant tumors. The majority synthesize estrogens; a few synthesize androgens. The most common estrogen-producing ovarian tumor causing precocious puberty is the granulosa cell tumor. Other tumors that can cause precocious puberty are thecomas, luteomas, mixed types, theca-lutein and follicular cysts, and ovarian tumors (i.e., teratoma, choriocarcinoma, and dysgerminoma).

**ESTROGENIC LESIONS OF THE OVARY**

These lesions cause isosexual precocious sexual development but account for only a small percentage of all cases of precocity. Benign ovarian follicular cysts are the most common tumors associated with isosexual precocious puberty in girls; they may rarely be gonadotropin dependent. Gonadotropin-independent follicular cysts that produce estrogen are often associated with the McCune-Albright syndrome.

**Juvenile Granulosa Cell Tumor**

In childhood, the most common neoplasm of the ovary with estrogenic manifestations is the granulosa cell tumor, although it makes up only 1-10% of all ovarian tumors. These tumors have distinctive histologic features that differ from those encountered in older women (adult granulosa cell tumor). The cells have high mitotic activity, follicles are often irregular, Call-Exner bodies are rare, and luteinization is frequent. The tumor may be solid or cystic, or both. It usually is benign. In a few instances, this tumor has been associated with multiple enchondromas (Ollier disease) and, in fewer still, with multiple subcutaneous hemangiomas (Maffucci syndrome).

**Clinical Manifestations and Diagnosis**

The juvenile granulosa cell tumor has been observed in newborns and may manifest with sexual precocity at 2 yr of age or younger; about half these tumors occurred before 10 yr of age. The mean age at diagnosis is 7.5 yr. The tumors are almost always unilateral. The breasts become enlarged, rounded, and firm, and the nipples prominent. The external genitals resemble those of a normal girl at puberty, and the uterus is enlarged. A white vaginal discharge is followed by irregular or cyclic menstruation. Ovulation, however, does not occur. The presenting manifestation may be abdominal pain or swelling. Pubic hair is usually absent unless there is mild virilization.

A mass is readily palpable in the lower portion of the abdomen in most children by the time sexual precocity is evident. The tumor may be small, however, and escape detection even on careful rectal and abdominal examination; the tumors may be detected by ultrasonography, but multidetector CT scans are most sensitive. Most such tumors (90%) are diagnosed at very early stages of malignancy. Plasma estradiol levels are markedly elevated. Plasma levels of gonadotropins are suppressed and do not respond to gonadotropin-releasing hormone analog stimulation. Levels of antimüllerian hormone, inhibin B, and α-fetoprotein may be elevated. Activating mutations of Gαs are seen in 30%, and GATA-4 expression is retained in the more aggressive tumors while antimüllerian hormone levels are inversely proportional to tumor size. Osseous development is moderately advanced. Several case reports showing the association of 45,X/46,XY karyotype and ambiguous genitalia with ovarian granulosa tumor have been published in literature.

**Treatment and Prognosis**

The tumor should be removed as soon as the diagnosis is established. Prognosis is excellent because fewer than 5% of these tumors in children are malignant. Advanced-stage tumors, however, behave aggressively and require difficult decisions regarding surgical approaches as well as the use of irradiation and chemotherapy. In adults with granulosa cell tumors, p53 expression is associated with unfavorable prognosis. Vaginal bleeding immediately after removal of the tumor is common. Signs of precocious puberty abate and may disappear within a few months after the operation. The secretion of estrogens returns to normal.

Sex cord tumor with annular tubules is a distinctive tumor, thought to arise from granulosa cells, that occurs primarily in patients with Peutz-Jeghers syndrome. These tumors are multifocal, bilateral, and usually benign. The presence of calcifications aids ultrasonographic detection. Increased aromatase production by these tumors results in gonadotropin-independent precocious puberty. Inhibin A and B levels
are elevated and decrease after tumor removal. In 1 study, 9 of 13 sex
cord/stromal tumors exhibited follicle-stimulating hormone receptor
mutations, suggesting a role for such mutation in the development of
these tumors.

Chorioepithelioma has been reported only rarely. This highly malig
nant tumor is thought to arise from a preexisting teratoma. The usually
unilateral tumor produces large amounts of human chorionic gonado
tropin, which stimulates the contralateral ovary to secrete estrogen.
Elevated levels of human chorionic gonadotropin are diagnostic.

Follicular Cyst
Small ovarian cysts (<0.7 cm in diameter) are common in prepubertal
children. At puberty and in girls with true isosexual precocious
puberty, larger cysts (1-6 cm) are often seen; these are secondary to
stimulation by gonadotropins. However, similar larger cysts occur
occasionally in young girls with precocious puberty in the absence of
lutestiminating hormone and follicle-stimulating hormone. Because surgi
cal removal or spontaneous involution of these cysts results in regres
sion of pubertal changes, there is little doubt that they are its cause.
The mechanism of production of these autonomously functioning
cysts is unknown. Such cysts may form only once, or they may disap
pear and recur, resulting in waxing and waning of the signs of precoc
ious puberty. They may be unilateral or bilateral. The sexual precocity
that occurs in young girls with McCune-Albright syndrome is usually
associated with autonomous follicular cysts caused by a somatic
activating mutation of the Gα protein occurring early in development
(see Chapter 562.6). Gonadotropins are suppressed, and estradiol
levels are often markedly elevated, but they may fluctuate widely and
even temporarily may return to normal. Gonadotropin-releasing
hormone analog stimulation fails to evoke an increase in gonadotro
pins. Ultrasonography is the method of choice for the detection and
monitoring of such cysts. Aromatase inhibitors are shown to be the
mainstay of the therapy in females with McCune-Albright syndrome
and persistent estradiol elevation. A short period of observation to
ascertain the lack of spontaneous resolution is advisable before cyst
aspiration or cystectomy is considered. Cystic neoplasms must be con
sidered in the differential diagnosis.

ANDROGENIC LESIONS OF THE OVARY
Virilizing ovarian tumors are rare at all ages but particularly so in
prepubertal girls. Arrhenoblastoma has been reported as early as 14
days of age, but few cases have been reported in girls younger than
16 yr of age.

The gonadoblastoma occurs exclusively in dysgenetic gonads, par
pecially in phenotypic females who have a Y chromosome or a Y
fragment in their genotype (46,XY; 45,X/46,XY; 45,X/46,X-fra). As
noted above, there is a proposed gonadoblastoma locus on the Y chro
mosome (GBY). The tumors may be bilateral. Virilization occurs with
some but not all tumors. The clinical features are the same as those
seen in patients with virilizing adrenal tumors and include accelerated
growth, acne, clitoral enlargement, and growth of sexual hair. A pal
pable, abdominal mass is found in about 50% of patients. Plasma levels
of testosterone and androstenedione are elevated, and gonadotropins
are suppressed. Ultrasonography, CT, and MRI usually localize the
lesion. The dysgenetic gonad of phenotypic females with a Y chro
some or fragment of Y chromosome containing GBY should be
removed prophylactically. When a unilateral tumor is removed, the
contralateral dysgenetic gonad should also be removed. Association of
gonadoblastoma and WAGR (Wilms, aniridia, genitourinary anom
alies, mental retardation) syndrome is also reported in the literature. In
an immunohistochemical study of 2 gonadoblastomas, expressions of
WT1, p53, and MIS, as well as inhibin, were all demonstrated.

Virilizing manifestations occur occasionally in girls with juvenile
granulosa cell tumors. Adrenal rests and hilum cell tumors rarely lead
to virilization. Activating mutations of G-protein genes have been
described in ovarian (and testicular) tumors. Gα mutations, usually
seen in gonadal tumors associated with McCune-Albright syndrome,
were also noted in 4 of 6 Leydig cell tumors (3 ovarian, 1 testicular).
Two granulosa cell tumors and 1 thecoma of 10 ovarian tumors studied
were found to have GIP-2 mutations.

Sertoli-Leydig cell tumors, rare sex cord/stromal neoplasms, con
stitute less than 1% of ovarian tumors. The average age at diagnosis is
25 yr; less than 5% of these tumors occur before puberty. α-Fetoprotein
levels may be mildly elevated. In one 12 mo old with Sertoli-Leydig
cell tumor presenting with isosexual precocity the only detectable
malignant marker was the serum inhibin level, with elevations in both A
and B subunits. Five-year survival rates are 70-90%.

Of 102 consecutive patients who underwent surgery because of
ovarian masses over a 15 yr period, the presenting symptoms were
acute abdominal pain in 56% and abdominal or pelvic mass in 22%.
Of 9 children whose cause for surgery was presumed malignancy, 3
had dysgerminomas, 2 had teratomas, 2 had juvenile granulosa cell
tumors, 1 had a Sertoli-Leydig cell tumor, and 1 had a yolk sac tumor.

Bibliography is available at Expert Consult.
Bibliography
SEX DIFFERENTIATION

See also Chapter 582.

In normal differentiation, the final form of all sexual structures is consistent with normal sex chromosomes (either XX or XY). A 46,XX complement of chromosomes as well as genetic factors such as DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), the signaling molecule WNT-4, and R-Spondin1 are among the many needed for the development of normal ovaries. Development of the male phenotype is potentially more complex. It requires a Y chromosome and, specifically, an intact SRY (sex-determining region on the Y chromosome) gene, which, in association with other genes such as SOX9, SF-1 (steroidogenic factor-1), WT1 (Wilms tumor 1), and others (see Chapter 582), directs the undifferentiated gonad to become a testis. Aberrant recombinations may result in X chromosomes carrying SRY, resulting in XX males, or Y chromosomes that have lost SRY, resulting in XY females. Epigenetic causes of abnormal sex differentiation have been shown in plants, invertebrates, and vertebrates, and will likely contribute to human disorders of sex development (DSDs) as well.

Antimüllerian hormone (AMH) causes the müllerian ducts to regress; in its absence, they persist as the uterus, fallopian tubes, cervix, and upper vagina. AMH activation in the testes may require the SF-1 gene. By about 8 wk of gestation, the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG), which peaks at 8-12 wk. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. Testosterone produced locally initiates development of the ipsilateral wolffian duct into the epididymis, vas deferens, and seminal vesicle. Development of the external genitalia also requires dihydrotestosterone (DHT), the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary to fuse the genital folds to form the penis and scrotum. DHT is also produced via an alternative biosynthetic pathway from androstanediol, and this pathway must be intact for normal and complete prenatal virilization to occur. A functional androgen receptor, produced by an X-linked gene, is required for testosterone and DHT to induce these androgen effects.

In the XX fetus with normal long and short arms of the X chromosome, the bipotential gonad develops into an ovary by about the 10th-11th wk. This occurs only in the absence of SRY, testosterone, and AMH and requires a normal gene in the dosage-sensitive/sex-reversal
loca DAX1, the WNT-4 molecule, and R-Spondin1. A female external phenotype develops in the absence of fetal gonads. However, the male phenotype development requires androgen production and action. Estrogen is unnecessary for normal prenatal sexual differentiation, as demonstrated by 46,XX patients with aromatase deficiency and by mice without estradiol receptors.

Chromosomal aberrations may result in ambiguity of the external genitalia. Conditions of aberrant sex differentiation may also occur with the XX or XY genotype. The appropriate term for what was previously called intersex is DSD. This term defines a condition “in which development of chromosomal, gonadal, or anatomical sex is atypical.” It is increasingly preferable to use the term “atypical genitalia” rather than “ambiguous genitalia.” Tables 588-1 and 588-2 compare previous terms with their revised etiologic classification nomenclature. Table 582-1 in Chapter 582 lists some of the genes that are mutated in various forms of DSD.

The definition of atypical or ambiguous genitalia, in a broad sense, is any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations in size of these structures do not always constitute ambiguity.

Development of the external genitalia begins with the potential to be either male or female (Fig. 588-1). Virilization of a female, the most common form of DSD, results in varying phenotypes (Fig. 588-2), that develop from the basic bipotential genital appearances of the embryo (Fig. 588-1).

**DIAGNOSTIC APPROACH TO THE PATIENT WITH ATYPICAL OR AMBIGUOUS GENITALIA**

The appearance of the external genitalia is rarely diagnostic of a particular disorder, and thus does not often allow distinction among the various forms of DSD. The most common forms of 46,XX DSD are virilizing forms of congenital adrenal hyperplasia. It is important to note that in 46,XY DSD, the specific diagnosis is not found in up to 50% of cases; partial androgen insensitivity syndrome and pure gonadal dysgenesis are common identifiable etiologies in XY DSD. At 1 center with a large experience, the etiologies of DSD in 250 patients over 25 yr were compiled. The 6 most common diagnoses accounted for 50% of the cases. These included virilizing congenital adrenal hyperplasia (14%), androgen insensitivity syndrome (10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46,XY small-for-gestational-age males with hypospadias (6%).

The relative lack of established diagnoses in 46,XY DSD and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects in each patient with genital ambiguity. The parents need counseling about the potentially complex nature of the baby’s condition, and guidance as to how to deal with their well-meaning but curious friends and family members. The

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**Table 588-1** Revised Nomenclature

<table>
<thead>
<tr>
<th>PREVIOUS</th>
<th>CURRENTLY ACCEPTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intersex</td>
<td>Disorders of sex development (DSD)</td>
</tr>
<tr>
<td>Male pseudohermaphrodite</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>Undervirilization of an XY male</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>Undermasculinization of an XY male</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>46,XY intersex</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>Female pseudohermaphrodite</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>Overmasculinization of an XX female</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>Masculinization of an XX female</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>46,XX intersex</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>True hermaphrodite</td>
<td>Ovotesticular DSD</td>
</tr>
<tr>
<td>Gonadal intersex</td>
<td>Ovotesticular DSD</td>
</tr>
<tr>
<td>XX male or XX sex reversal</td>
<td>46,XX testicular DSD</td>
</tr>
<tr>
<td>XY sex reversal</td>
<td>46,XY complete gonadal dysgenesis</td>
</tr>
</tbody>
</table>


**Table 588-2** Etiologic Classification of Disorders of Sex Development (DSD)

46,XX DSD

- **Androgen Exposure**
  - **Fetal/Fetoplacental Source**
    - 21-Hydroxylase (P450c21 or CYP21) deficiency
    - 11β-Hydroxylase (P450c11 or CYP11B1) deficiency
    - 3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency
  - Cytochrome P450 oxidoreductase (POR)
  - Aromatase (P450arom or CYP19) deficiency
  - Glucocorticoid receptor gene mutation
- **Maternal Source**
  - Virilizing ovarian tumor
  - Virilizing adrenal tumor
  - Androgenic drugs
- **Disorder of Ovarian Development**
  - XX gonadal dysgenesis
  - Testicular DSD (SRY+, SOX9 duplication)
- **Undetermined Origin**
  - Associated with genitourinary and gastrointestinal tract defects

46,XY DSD

- **Defects in Testicular Development**
  - Denys-Drash syndrome (mutation in WT1 gene)
  - WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation)
  - Deletion of 11p13
  - Campomelic syndrome (autosomal gene at 17q24.3–q25.1) and SOX9 mutation
  - XY pure gonadal dysgenesis (Soyer syndrome)
  - Mutation in SRY gene
  - XY gonadal agenesis
  - Unknown cause
- **Deficiency of Testicular Hormones**
  - Leydig cell aplasia
  - Mutation in LH receptor
  - Lipoid adrenal hyperplasia (P450sc or CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein)
  - 3β-HSD II deficiency
  - 17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency
  - Persistent müllerian duct syndrome because of antimüllerian hormone gene mutations or receptor defects for antimüllerian hormone
- **Defect in Androgen Action**
  - Dihydrotestosterone deficiency because of 5α-reductase II mutations or AKR1C2/AKR1C4 mutations
  - Androgen receptor defects:
    - Complete androgen insensitivity syndrome
    - Partial androgen insensitivity syndrome
    - (Reifenstein and other syndromes)
    - Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHC7)
- **Ovotesticular DSD**
  - XX
  - XY
  - XX/XY chimeras
- **Sex Chromosome DSD**
  - 45,X (Turner syndrome and variants)
  - 47,XY (Klinefelter syndrome and variants)
  - 45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
  - 46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

Figure 588-1 Schematic demonstration of differentiation of normal male and female genitalia during embryogenesis. (From Zitelli BJ, Davis HW: Atlas of pediatric physical diagnosis, ed 4, St. Louis, 2002, Mosby, p. 328.)

Figure 588-2 Examples of atypical genitalia. These cases include ovotesticular disorder of sexual development (A) and congenital virilizing adrenal hyperplasia (B-E). (B-D courtesy of D. Becker, MD, Pittsburgh. From Zitelli BJ, Davis HW: Atlas of pediatric physical diagnosis, ed 4, St. Louis, 2002, Mosby, p. 329.)
evaluation and management should be carried out by a multidisciplinary team of experts that includes pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine, genetics, and psychology. Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical exam, the common diagnostic approach includes multiple steps, described in the following outline. These steps are usually performed simultaneously rather than waiting for results of 1 test prior to performing another, because of the sensitive and sometimes urgent nature of the condition. Careful attention to the presence of physical features other than the genitalia is crucial, to determine if a diagnosis of a particular multisystem syndrome is possible. These are described in more detail in Chapters 588.1, 588.2, and 588.3 below. Table 588-3 summarizes many of the features of commonly encountered causes of DSD.

Diagnostic tests include the following:
1. Karyotype, with rapid determination of sex chromosomes (in many centers this is available within 24-48 hr)
2. Other blood tests
   a. Screen for congenital adrenal hyperplasia: cortisol biosynthetic precursors and adrenal androgens (particularly 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form)
   b. Screen for androgens and their biosynthetic precursors
   c. Screen for gonadal response to gonadotropin in patients suspected of having testicular gonads: stimulation with injections of hCG; measure testosterone and DHT before and after hCG
   d. Molecular genetic analyses for SRY and other Y-specific loci
   e. Gonadotropin levels
3. The internal anatomy of patients with ambiguous genitalia can be defined with 1 or more of the following studies:
   a. Voiding cystourethrogram
   b. Endoscopic examination of the genitourinary tract
   c. Pelvic ultrasound; renal and adrenal ultrasound
   d. Pelvic CT or MRI
   e. Exploratory laparoscopy

Table 588-3 | Ambiguous Genitalia: Steps in Establishing the Diagnosis

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>21-OH DEFICIENCY</th>
<th>GONADAL DYSGENESIS WITH Y CHROMOSOME</th>
<th>OVOTESTICULAR DSD</th>
<th>PARTIAL ANDROGEN INSENSITIVITY</th>
<th>BLOCK IN TESTOSTERONE SYNTHESIS</th>
</tr>
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<tbody>
<tr>
<td>Palpable gonad(s)</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Uterus present*</td>
<td>+</td>
<td>+</td>
<td>Usually</td>
<td>–</td>
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</tr>
<tr>
<td>Increased skin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sick baby</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dysmorphic features</td>
<td>–</td>
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**DIAGNOSTIC CONSIDERATIONS**

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<th>GONADAL DYSGENESIS WITH Y CHROMOSOME</th>
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<th>PARTIAL ANDROGEN INSENSITIVITY</th>
<th>BLOCK IN TESTOSTERONE SYNTHESIS</th>
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<td>Serum 17-OHP Elevated</td>
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<td>Normal</td>
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<td>Electrolytes</td>
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<td>Karyotype</td>
<td>46,XX</td>
<td>45,XY/46,XY or others</td>
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<tr>
<td>Testosterone response to hCG</td>
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<td>Positive</td>
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<td>Positive response</td>
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<td>Gonadal biopsy</td>
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<tr>
<td>Other testing</td>
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</table>

*As determined by ultrasound or rectal examination.

AR, androgen receptor; DSD, disorders of sex development; hCG, human chorionic gonadotropin; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NA, not applicable.


588.1 46,XX DSD

Patricia A. Donohoue

In this condition, the genotype is XX and the gonads are ovaries but the external genitalia are virilized. There is no significant AMH production because the gonads are ovaries. Thus the uterus, fallopian tubes, and cervix develop. The varieties and causes of this condition are relatively few. Most instances result from exposure of the female fetus to excessive exogenous or endogenous androgens during intrauterine life. The changes consist principally of virilization of the external genitalia (clitoral hypertrophy and labioscrotal fusion).

CONGENITAL ADRENAL HYPERPLASIA

See Chapter 576.1.

This is the most common cause of genital ambiguity and of 46,XX DSD. Females with the 21-hydroxylase and 11-hydroxylase defects are the most highly virilized, although minimal virilization also occurs with the type II 3β-hydroxysteroid dehydrogenase defect (see Fig. 588-1). Female patients with salt-losing congenital adrenal hyperplasia tend to have more virilization than do non–salt-losing patients. Masculinization may be so intense that a complete penile urethra results, and the patient may appear to be a male with bilateral cryptorchidism.

AROMATASE DEFICIENCY

In genotypic females, the rare condition of aromatase deficiency during fetal life leads to 46,XX DSD and results in hypergonadotropic hypogonadism at puberty because of ovarian failure to synthesize estrogen.

Two 46,XX infants had enlargement of the clitoris and posterior labial fusion at birth. In 1 instance, maternal serum and urinary levels of estrogen were very low and serum levels of androgens were high. Cord serum levels of estrogen were also extremely low, but those of androgen were elevated. The second patient also had virilization of unknown cause since birth, but the aromatase deficiency was not diagnosed until 14 yr of age, when she had further virilization and failed to go into puberty. At that time, she had elevated levels of gonadotropins and androgens but low estrogen levels, and ultrasonography...
revealed large ovarian cysts bilaterally. These 2 patients demonstrate the important role of aromatase in the conversion of androgens to estrogens. Additional female and male patients with aromatase deficiency as a consequence of mutations in the aromatase gene (CYP19) are known. Two siblings were described. The 28 yr old XX proband was 177.6 cm tall (+2.5 SD) after having received hormonal replacement therapy; her 24 yr old brother was 204 cm tall (+3.7 SD), and had a bone age of 14 yr. Low-dose estradiol replacement, carefully adjusted to maintain normal age-appropriate levels, may be indicated for affected females, even prepubertally.

GLUCOCORTICOID RECEPTOR GENE MUTATION
A 9 yr old girl with 46,XX disorder of sexual development, thought to be caused by 21-hydroxylase deficiency (congenital adrenal hyperplasia) since the age of 5 yr, had elevated cortisol levels both at baseline and after dexamethasone, hypertension, and hypokalemia, suggestive of the diagnosis of generalized glucocorticoid resistance. A novel homozygous mutation in exon 5 of the glucocorticoid receptor was demonstrated. In this Brazilian family, the condition was autosomal recessive.

Cytochrome P450 oxidoreductase, encoded by a gene on 7q11.2, is a cofactor implicated in combined P450C17 and P450C21 steroidogenic defects. Girls are born with ambiguous genitalia, but the virilization does not progress postnatally and androgen levels are normal or low. Boys may be born undervirilized. Both may exhibit bony abnormalities seen in Antley-Bixler syndrome. Conversely, in a series of Antley-Bixler syndrome patients, those with ambiguous genitalia and disordered steroidogenesis had cytochrome P450 oxidoreductase deficiency. Those without genital ambiguity with normal steroidogenesis had fibroblast growth factor receptor 2 (FGFR2) mutations. The cardinal features of Antley-Bixler syndrome include craniosynostosis, severe midface hypoplasia, proptosis, choanal atresia/stenosis, frontal bossing, dysplastic ears, depressed nasal bridge, radioulnar synostosis, long bone fractures and femoral bowing, and urogenital abnormalities.

VIRILIZING MATERNAL TUMORS
Rarely, the female fetus has been virilized during fetal life by a maternal androgen-producing tumor. In a few cases, the lesion was a benign adrenal adenoma, but all others were ovarian tumors, particularly androblastomas, luteomas, and Krukenberg tumors (Table 588-4). Maternal virilization may be manifested by enlargement of the clitoris, acne, deepening of the voice, decreased lactation, hirsutism, and elevated levels of androgens. In the infant, there is enlargement of the clitoris of varying degrees, often with labial fusion. Mothers of children with unexplained 46,XX DSD should undergo physical examination and measurements of their own levels of plasma testosterone, dehydroepiandrosterone sulfate, and androstenedione.

ADMINISTRATION OF ANDROGENIC DRUGS TO WOMEN DURING PREGNANCY
Testosterone and 17-methyltestosterone have been reported to cause 46,XX DSD in some instances (see Table 588-4). The greatest number of cases has resulted from the use of certain progestational compounds for the treatment of threatened abortion. These progestins have been replaced by nonvirilizing ones.

Infants with virilization and 46,XX chromosomes and caudal anomalies have been reported for whom no virilizing agent could be identified. In such instances, the disorder is usually associated with other congenital defects, particularly of the urinary and gastrointestinal tracts. Y-specific DNA sequences, including SRY, are absent. In 1 case, a scrotal raphe and elevated testosterone levels were found, but the cause remains unknown.

Bibliography is available at Expert Consult.

588.2 46,XY DSD
Patricia A. Donohoue

In this condition, the genotype is XY but the external genitalia are either not completely virilized, are ambiguous (atypical), or are completely female. When gonads can be found, they invariably contain testicular elements; their development ranges from rudimentary to normal. Because the process of normal virilization in the fetus is so complex, it is not surprising that there are many varieties and causes of 46,XY DSD. As noted earlier, the etiology of 46,XY DSD is not identified in approximately 50% of cases.

DEFECTS IN TESTICULAR DIFFERENTIATION
The first step in male differentiation is conversion of the bipotential gonad into a testis. In the XY fetus, if there is a deletion of the short arm of the Y chromosome or of the SRY gene, male differentiation does not occur. The phenotype is female; müllerian ducts are well developed because of the absence of AMH, and gonads consist of undifferentiated streaks. By contrast, even extreme deletions of the long arm of the Y chromosome (Yq−) have been found in normally developed males, most of whom are azoospermic and have short stature. This indicates that the long arm of the Y chromosome normally has genes that prevent these manifestations. In many syndromes in which the testes fail to differentiate, Y chromosomes are morphologically normal.

Denys-Drash Syndrome
The constellation of nephropathy with ambiguous genitalia and bilateral Wilms tumor is the major phenotype of this syndrome. Most reported cases have been 46,XY. Müllerian ducts are often present, indicating a global deficiency of fetal testicular function. Patients with a 46,XX karyotype have normal external genitalia. The onset of proteinuria in infancy progresses to nephrotic syndrome and end-stage renal failure by 3 yr of age, with focal or diffuse mesangial sclerosis being the most consistent histopathologic finding. Wilms tumor usually develops in children younger than 2 yr of age and is frequently bilateral. Gonadoblastomas have also been reported.

Several mutations of the WT1 gene, located on chromosome 11p13, have been found. WT1 functions as a tumor-suppressor gene and a transcriptional factor, and is expressed in the genital ridge and fetal gonads. Nearly all reported mutations have been near or within the zinc finger–coding region. One report found a zinc finger domain mutation in the WT1 allele of a patient with no genital urinary abnormalities, suggesting that some cases of sporadic Wilms tumor may carry the WT1 mutation. Different mutations of the WT1 gene, con-

Table 588-4 Sources of Maternal-Derived Androgens

<table>
<thead>
<tr>
<th>ENDogenous</th>
<th>SYNTHETIC ANDROGENS</th>
<th>EXOGENOUS</th>
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<td>BENIGN</td>
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<td>Danazol</td>
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<td>Adrenal adenoma</td>
<td>Progestins</td>
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<td>Hyperreactio lutealis</td>
<td>(medroxyprogesterone acetate)</td>
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<tr>
<td>Thecoma/fibroma</td>
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<td>Stromal hyperthecosis</td>
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<td>Brenner tumor</td>
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<tr>
<td>Mature cystic teratoma</td>
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<tr>
<td>(dermoid cyst)</td>
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<tr>
<td>MALIGNANT</td>
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<tr>
<td>Metastatic carcinomas</td>
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<tr>
<td>(Krukenberg tumor)</td>
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<tr>
<td>Sex-cord stromal tumors—granulosa cell and Sertoli-Leydig tumors</td>
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<tr>
<td>Adrenal cortical carcinoma</td>
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<tr>
<td>Cystadenocarcinoma</td>
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<tr>
<td>Hilar cell tumor</td>
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</tbody>
</table>

Bibliography
stational heterozygote mutations at intron 9, have been described in Fraser syndrome, a condition of nonspecific focal and segmental glomerulosclerosis, 46,XY gonadal dysgenesis, and frequent gonadoblastoma, but without Wilms tumor.

**WAGR Syndrome**

This acronymic contiguous gene syndrome consists of Wilms tumor, aniridia, genitourinary malformations, and retardation (WAGR). These children have a deletion of 1 copy of chromosome 11p13, which may be visible on karyotype analysis. The deleted region encompasses the aniridia gene (PAX6) and the Wilms tumor-suppressor gene (WT1). Only the 46,XY males have genital abnormalities, ranging from cryptorchidism to severe deficiency of virilization. Gonadoblastomas have developed in the dysgenetic gonads. Wilms tumor usually occurs by 2 yr of age. Some cases also had unexplained obesity, raising the question of an obesity-associated gene in this region of chromosome 11 and naming the syndrome WAGRO.

**Campomelic Syndrome**

See Chapter 704.

This form of short-limbed dysplasia is characterized by anterior bowing of the femur and tibia, small, bladeless scapulae, small thoracic cavities, and 11 pairs of ribs, along with malformations of other organs. It is usually lethal in early infancy. Approximately 75% of reported 46,XY patients exhibit a completely female phenotype; the external and internal genitalia are female. Some 46,XY patients have ambiguous genitals. The gonads appear to be ovaries but histologically may contain elements of both ovaries and testes.

The gene responsible for the condition is SOX9 (SRY-related HMG [high-mobility group]-box gene) and is on 17q24-q25. This gene is structurally related to SRY and also directly regulates development of the type II collagen gene (COL2A1). The same mutations may result in different gonadal phenotypes. Gonadoblastoma was reported in a patient with this condition. The inheritance is autosomal dominant. Adrenal insufficiency and 46,XY gonadal dysgenesis has been described in patients with mutations of the SF-1 gene. In some of these patients, if the mother shares the SF-1 mutation, she has premature ovarian insufficiency.

46,XY sex reversal has been described in patients with deletions of parts of autosomal loci on chromosomes 2q, 9p, and 10q.

**XY Pure Gonadal Dysgenesis (Swer Syndrome)**

The designation “pure” distinguishes this condition from forms of gonadal dysgenesis that are of chromosomal origin and associated with somatic anomalies. Affected patients have normal stature and a female phenotype, including vagina, uterus, and fallopian tubes, but at puberty, breast development and menarche fail to occur. None of the other phenotypic features associated with 45,X are present. Patients present at puberty with hypergonadotropic primary amenorrhea. Familial cases suggest an X-linked or a sex-limited dominant autosomal transmission. Most of the patients examined have had mutations of the SRY gene. None had a SOX9 gene mutation. The gonads consist of almost totally undifferentiated streaks despite the presence of a cytogenetically normal Y chromosome. The primitive gonad cannot accomplish any testicular function, including suppression of müllerian ducts. There may be hilar cells in the gonad capable of producing some androgens; accordingly, some virilization, such as clitoral enlargement, may occur at the age of puberty. The streak gonads may undergo neo-

**LEMD TESTICULAR HORMONES**

Five genetic defects have been delineated in the enzymatic synthesis of testosterone by the fetal testis, and a defect in Leydig cell differentiation has been described. These defects produce 46,XY males with inadequate masculinization (see Fig. 582-1 in Chapter 582). Because levels of testosterone are normally low before puberty, an hCG stimulation test may be needed in children to assess the ability of the testes to synthesize testosterone.

**Leydig Cell Aplasia**

Patients with aplasia or hypoplasia of the Leydig cells usually have female phenotypes, but there may be mild virilization. Testes, epididymis, and vas deferens are present; the uterus and fallopian tubes are absent because of normal production of AMH. There are no secondary sexual changes at puberty, but pubic hair may be normal. Plasma levels of testosterone are low and do not respond to hCG; LH levels are elevated. The Leydig cells of the testes are absent or markedly deficient. The defect may involve a lack of receptors for LH. In children, hCG stimulation is necessary to differentiate the condition from the androgen insensitivity syndromes (AISs). There is male-limited autosomal recessive inheritance. The human LH receptor is a member of the G-protein–coupled superfamily of receptors that contains 7 transmembrane domains. Several inactivating mutations of the LH receptor have been described in males with hypogonadism suspected of having Leydig cell hypoplasia or aplasia.

High serum LH and low follicle-stimulating hormone were noted in 1 male with hypogonadism owing to a mutation in the gene for the β-subunit of follicle-stimulating hormone (see Table 583-1 in Chapter 583).

**Lipoid Adrenal Hyperplasia**

See Chapter 576.

The most severe form of congenital adrenal hyperplasia derives its name from the appearance of the enlarged adrenal glands resulting from accumulation of cholesterol and cholesterol esters. The rate-limiting process in steroidogenesis is the transport of free cholesterol
through the cytosol to the inner mitochondrial membrane, where the P450 side-chain cleavage enzyme (P450scc; CYP11A1) acts. Cholesterol transport into mitochondria is mediated by the steroidogenic acute regulatory protein (STAR) whose synthesis occurs via cyclic adenosine monophosphate through a cyclic adenosine monophosphate response element–binding protein. STAR is a 30 kDa protein essential for steroidogenesis and is encoded by a gene on chromosome 8p11.2. The mitochondrial content of STAR increases between 1 and 5 hr after adrenocorticotropic hormone stimulation, long after the acute adrenocorticotropic hormone–induced increase in steroidogenesis. This has led some to suggest that extramitochondrial STAR might also be involved in the acute response to adrenocorticotropic hormone.

All serum steroid levels are low or undetectable, whereas corticosterone and plasma renin levels are quite elevated. The phenotype is female in both genetic females and males. Genetic males have no Müllerian structures because the testes can produce normal AMH but no steroid hormones. These children present with acute adrenal crisis and salt wasting in infancy. Most patients are 46,XX. In a few patients, ovarian steroidogenesis is present at puberty.

The regulatory role of STAR-independent steroidogenesis is illustrated by 46,XX 4 mo old twins with lipoid adrenal hyperplasia. One died at 15 mo because of cardiac complications related to coarctation of the aorta. The adrenal glands had characteristic lipid deposits. The surviving twin had spontaneous puberty with feminization at 11.5 yr and menarche at 13.8 yr. When restudied at the age of 15 yr, a homozygous frameshift–inactivating mutation in her STAR gene was discovered. This and the fact that she survived as an infant until 4 mo of age without replacement therapy with detectable serum aldosterone levels supports the hypothesis that STAR-independent steroidogenesis was able to proceed until enough intracellular lipid accumulated to destroy steroidogenic activity. Partial defects in only partially virilized males and delayed onset of salt wasting have been described. Complete P450scc defects may be incompatible with life because only this enzyme can convert cholesterol to pregnenolone, which then becomes progesterone, a hormone essential for the maintenance of normal mammalian pregnancy. Heterozygous mutation in CYP11A1 was described in a 4 yr old with 46,XY sex reversal and late-onset form of lipoid adrenal hyperplasia. At 6-7 wk of gestation, when maternal corpus luteum progesterone synthesis stops, the placenta, which does not express STAR, produces progesterone by STAR-independent steroidogenesis using the CYP11A1 enzyme system.

**3β-Hydroxysteroid Dehydrogenase Deficiency**

Males with this form of congenital adrenal hyperplasia (see Chapter 576) have various degrees of hypoaldosteronism, with or without bimodal serum and cryptorchidism and, rarely, a complete female phenotype. Affected infants usually develop salt-losing manifestations shortly after birth. Incomplete defects, occasionally seen in boys with premature pubarche, as well as late-onset nonclassic forms, have been reported. These children have point mutations of the gene for type II 3β-hydroxysteroid dehydrogenase, which becomes progesterone to androstenedione, a male hormone essential for the maintenance of normal mammalian pregnancy. Heterozygous mutations in CYP11A1 were described in a 4 yr old with 46,XY sex reversal and late-onset form of lipoid adrenal hyperplasia. At 6-7 wk of gestation, when maternal corpus luteum progesterone synthesis stops, the placenta, which does not express STAR, produces progesterone by STAR-independent steroidogenesis using the CYP11A1 enzyme system.

**Deficiency of 17-Ketosteroid Reductase**

This enzyme, also called 17β-hydroxysteroid dehydrogenase, catalyzes the final step in testosterone biosynthesis. It is necessary to convert androstenedione to testosterone and also dehydroepiandrosterone to androstenediol and estrone to estradiol. Enzymatic defects in the fetal testis give rise to males with complete or near-complete female phenotype in 46,XY males. Müllerian ducts are absent, and a shallow vagina is present. The diagnosis is based on the ratio of androstenedione to testosterone; in prepubertal children, stimulation with hCG may be necessary to make the diagnosis.

The defect is inherited in an autosomal recessive fashion. At least 4 different types of 17β-hydroxysteroid dehydrogenase are recognized, each coded by a different gene or different chromosomes. Type III is the enzyme defect that is especially common in a highly inbred Arab population in Gaza. The gene for the disorder is at 9q22 and is expressed only in the testes, where it converts androstenedione to testosterone. Most patients are diagnosed at puberty because of virilization and the failure to menstruate. Testosterone levels at puberty may approach normal, presumably as a result of peripheral conversion of androstenedione to testosterone; at this time, some patients spontaneously adopt a male gender role.

Type I 17β-hydroxysteroid dehydrogenase, encoded by a gene on chromosome 17q21, converts estrone to estradiol and is found in placenta, ovary, testis, liver, prostate, adipose tissue, and endometrium. Type II, whose gene is on chromosome 16q24, reverses the reactions of types I and III (converting testosterone to androstenedione and estrone to estradiol, respectively). Type IV is similar in action to type II. A late-onset form of 17-ketosteroid reductase deficiency presents as gynecomastia in young adult males.

**Persistent Müllerian Duct Syndrome**

In this disorder, there is persistence of Müllerian duct derivatives in otherwise completely virilized males. Cases have been reported in siblings and identical twins. Cryptorchidism is present in 80% of affected males; and during surgery for this or inguinal hernia, the condition is uncovered when a fallopian tube and uterus are found. The degree of Müllerian development is variable and may be asymmetric. Testicular function is normal in most, but testicular degeneration has been reported. Some affected males acquire testicular tumors after puberty. In a study of 38 families, 16 families had defects in the AMH gene, located on the short arm of chromosome 19. They had low AMH levels. In 16 families with high AMH levels, the defect was in the AMH type II receptor gene, with 10 of 16 having identical 27-bp deletions on exon 10 in at least 1 allele.

Treatment consists of removal of as many of the Müllerian structures as possible without causing damage to the testis, epididymis, or vas deferens.

**DEFECTS IN ANDROGEN ACTION**

In the following group of disorders, fetal synthesis of testosterone is normal and defective virilization results from inherited abnormalities in androgen action.
Dihydrotestosterone Deficiency

Decreased production of DHT in utero results in marked ambiguity of external genitalia of affected males. Biosynthesis and peripheral action of testosterone are normal.

The phenotype most commonly associated with this condition results in boys who have a small phallus, bifid scrotum, urogenital sinus with perineal hypospadias, and a blind vaginal pouch (Fig. 588-3). Testes are in the inguinal canals or labioscrotal folds and are normal histologically. There are no müllerian structures. Wolffian structures—the vas deferens, epididymis, and seminal vesicles—are present. Most affected patients have been identified as females. At puberty, virilization occurs: the phallus enlarges, the testes descend and grow normally, and spermatogenesis occurs. There is no gynecomastia. Beard growth is scanty, acne is absent, the prostate is small, and recession of the temporal hairline fails to occur. Virilization of the Wolffian duct is caused by the action of testosterone itself, although masculinization of the urogenital sinus and external genitals depends on the action of DHT during the critical period of fetal masculinization. Growth of facial hair and of the prostate also appears to be DHT dependent.

The adult height reached is close to that of the father and other male siblings. There is significant phenotypic heterogeneity. This has led to a classification of such patients into 5 types of steroid 5α-reductase deficiency (SRD).

Several different gene defects of SRD5A2 (the 5α-reductase type 2 gene leading to SRD) have been identified, located on the short arm of chromosome 2, in patients from throughout the world. Familial clusters have been reported from the Dominican Republic, Turkey, Papua New Guinea, Brazil, Mexico, and the Middle East. There is no reliable correlation between genotype and phenotype.

The disorder is inherited as an autosomal recessive trait but is limited to males; normal homozygous females with normal fertility indicate that in females DHT has no role in sexual differentiation or in ovarian function later in life. The clinical diagnosis should be made as early as possible in infancy. It is important to distinguish this from partial androgen insensitivity syndrome (PAIS), as patients with PAIS are far less sensitive to androgen than are patients with SRD. The biochemical diagnosis of SRD is based on finding normal serum testosterone levels, normal or low DHT levels with markedly increased basal and especially hCG-stimulated testosterone: DHT ratios (>17), and high ratios of urinary etiocholanolone to androsterone. Children with androgen insensitivity have normal hepatic 5α reduction and, thus, a normal ratio of tetrahydrocortisol to 5α-tetrahydrocortisol, as opposed to those with SRD.

It is important to note that most but not all children with SRD reared as females in childhood have changed to male around the time of puberty. It appears that exposures to testosterone in utero, neonatally, and at puberty have variable contributions to the formation of male gender identity. Much more needs to be learned about the influences of hormones such as androgens as well as the influences of cultural, social, psychologic, genetic, and other biologic factors in gender identity and behavior. Infants with this condition should be reared as boys whenever practical. Treatment of male infants with DHT results in phallic enlargement.

Another cause of DHT deficiency is a block in an alternative pathway of DHT synthesis. Patients previously thought to have 46,XY DSD because of isolated 17,20-lyase deficiency have subsequently been characterized as having mutations in the AKR1C2 gene (3α-reductase type 3) or both the AKR1C2 and AKR1C4 (3α-reductase type 4) genes. These findings showed that both the classical and alternative pathways to DHT must be intact for normal prenatal virilization.

Androgen Insensitivity Syndromes

The AISs are the most common forms of male DSD, occurring with an estimated frequency of 1/20,000 genetic males. This group of heterogeneous X-linked recessive disorders is caused by more than 150 different mutations in the androgen receptor gene, located on Xq11-12: single point mutations resulting in amino acid substitutions or premature stop codons, frameshift and premature terminations, gene deletions, and splice-site mutations.

Clinical Manifestations

The clinical spectrum of patients with AISs, all of whom have a 46,XY chromosomal complement, range from phenotypic females (in complete AIS) to males with various forms of ambiguous genitalia and undervirilization (partial AIS, or clinical syndromes such as Reifenstein syndrome) to phenotypically normal-appearing males with infertility. In addition to normal 46,XY chromosomes, the presence of testes and normal or elevated testosterone and LH levels are common to all such children (Figs. 588-4 and 588-5).

In complete androgen insensitivity syndrome (CAIS), an extreme form of failure of virilization, genetic males appear female at birth and are invariably reared accordingly. The external genitalia are female. The vagina ends blindly in a pouch, and the uterus is absent as a result of the normal production and effect of AMH by the testes. In about one third of patients, unilateral or bilateral fallopian tube remnants are found. The testes are usually intraabdominal but may descend into the inguinal canal; they consist largely of seminiferous tubules. At puberty, there is normal development of breasts and the habitus is female, but menstruation does not occur and sexual hair is absent. Adult heights of these women are commensurate with those of normal males despite profound congenital deficiency of androgenic effects.

The testes of affected adult patients produce normal male levels of testosterone, which are converted to normal levels of DHT. Failure of normal male differentiation during fetal life reflects a defective response to androgens at that time. The absence of androgenic effects is caused by a striking resistance to the action of endogenous or exogenous testosterone at the cellular level.

Prepubertal girls with this disorder are often detected when inguinal masses prove to be testes or when a testis is unexpectedly found during herniorrhaphy. Approximately 1-2% of girls with an inguinal hernia prove to have this disorder. In infants, elevated LH levels should suggest the diagnosis. In older girls and adults, amenorrhea is the usual presenting symptom. In prepubertal children, the condition must
be differentiated from other types of XY undervirilized males in which there is complete feminization. These include XY gonadal dysgenesis (Swerter syndrome), true agonadism, Leydig cell aplasia including LH receptor defects, and 17-ketosteroid reductase deficiency; all these conditions, unlike CAIS, are characterized by low levels of testosterone as neonates and during adult life and by failure to respond to hCG during the prepubertal years.

Although patients with CAIS have unambiguously female external genitals at birth, those with PAIS have a wide variety of phenotypic presentations, ranging from *perineoscrotal hypospadias*, bifid scrotum, and cryptorchidism to extreme undervirilization appearing as clitoromegaly and labial fusion. Some forms of PAIS are known as specific syndromes. Patients with *Reifenstein syndrome* have incomplete virilization characterized by hypogonadism, severe hypospadias, and gynecomastia (see Fig. 588-5). *Gilbert-Dreyfus* and *Lubs* syndromes are also classified as PAISs. In all cases, abnormalities in the androgen receptor gene have been identified. Table 588-5 lists other causes of a PAIS-like syndrome.

**Diagnosis**

The diagnosis of patients with PAIS may be particularly difficult in infancy. The postnatal surge in testosterone and LH is diminished in those with CAIS but not in those with PAIS. In some, especially those sufficiently virilized in infancy, the diagnosis is not suspected until puberty when there is inadequate virilization with lack of facial hair or voice change and the appearance of gynecomastia. Azoospermia and infertility are common. Increasingly, androgen receptor defects are being recognized in adults who have a small phallus and testes and infertility. A single-amino-acid substitution in the androgen receptor gene was reported in a large Chinese family in whom some affected members were fertile while others had gynecomastia and/or hypospadias. Production of insulin-like growth factor 2 and insulin-like growth factor–binding protein-2, but not insulin-like growth factor–binding protein-3, by genital skin fibroblasts is decreased in CAIS compared with normal genital skin fibroblasts, suggesting a possible role for the insulin-like growth factor system in modulating androgen action.
CAUSES OF A PAIS-LIKE PHENOTYPE

DEFECTS IN ANDROGEN PRODUCTION
- Partial gonadal dysgenesis
- Mutations in SRY, NR5A1, WT1
- Mutations of the luteinizing hormone receptor
- Biosynthetic enzyme deficiencies
- 17,20-Lyase deficiency
- P450 oxidoreductase deficiency
- 17β-hydroxysteroid dehydrogenase deficiency type 3
- 5α-Reductase deficiency type 2

GENETIC
- Klenefelter syndrome
- Smith-Lemli-Opitz syndrome
- Denys-Drash syndrome
- Frasier syndrome

PAIS
- Mutations of the androgen receptor gene
- Normal androgen receptor gene with fetal growth restriction

Table 588-5

<table>
<thead>
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<th>Causes of a PAIS-Like Phenotype</th>
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<td>DEFECTS IN ANDROGEN PRODUCTION</td>
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<td>• Partial gonadal dysgenesis</td>
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<td>• Mutations in SRY, NR5A1, WT1</td>
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<td>• 17β-hydroxysteroid dehydrogenase deficiency type 3</td>
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GENETIC
- Klenefelter syndrome
- Smith-Lemli-Opitz syndrome
- Denys-Drash syndrome
- Frasier syndrome

PAIS
- Mutations of the androgen receptor gene
- Normal androgen receptor gene with fetal growth restriction

NR5A1, nuclear receptor subfamily 5 A1; PAIS, partial androgen insensitivity syndrome; SRY, sex-determining region Y; WT1, Wilms tumor 1.


Treatment and Prognosis

In patients with CAIS whose sexual orientation is unambiguously female, the testes should be removed as soon as they are discovered. Laparoscopic removal of Y chromosome-bearing gonads has been performed in patients with AIS and in those with gonadal dysgenesis. In one third of patients, malignant tumors, usually seminomas, develop by 50 yr of age. Several teenage girls have acquired seminomas. Replacement therapy with estrogens is indicated at the age of puberty.

Normal breasts develop in affected girls who have not had their testes removed by the age of puberty. In these individuals, production of estradiol results from aromatase activity on testicular testosterone. The absence of androgenic activity also contributes to the feminization of these women.

The psychosexual and surgical management of patients with PAIS is extremely complex and depends in large part on the presenting phenotype. Osteopenia is recognized as a late feature of AIS.

Molecular analyses have suggested that phenotype may depend in part on somatic mosaicism of the androgen receptor gene. This was based on the case of a 46,XY patient who had a premature stop codon in exon 1 of the androgen receptor gene, but who also had evidence of virilization (pubic hair and clitoral enlargement) explained by the discovery of the wild-type alleles on careful examination of the sequenc- ing gel. The presence of mosaicism shifts the phenotype to a higher degree of virilization than expected from the genotype of the mutant allele alone.

Genetic counseling is difficult in families with androgen receptor gene mutation. In addition to lack of genotype–phenotype correlations, there is a high rate (27%) of de novo mutations in families.

Sex hormone–binding globulin reduction after exogenous androgen administration (stanozolol) correlates with the severity of the receptor defect and may become a useful clinical tool. Successful therapy with supplemental androgens has been reported in patients with PAIS and various mutations of the androgen receptor in the DNA-binding domain and the ligand-binding domain.

Mutated androgen receptors are also reported in patients with spinal and bulbar muscular atrophy in whom clinical manifestations including testicular atrophy, infertility, gynecomasia, and elevated LH, follicle-stimulating hormone, and estradiol levels usually manifest between the 3rd and 5th decades of life. Androgen receptor mutations have also been described in patients with prostate cancer.

UNDETERMINED CAUSES

Other XY undervirilized males display great variability of the external and internal genitalia and various degrees of phallic and müllerian development. Testes may be histologically normal or rudimentary, or there may only be 1. No recognized cause is identified in up to 50% of children with 46,XY DSD. Some ambiguity of the genitalia is associated with a wide variety of chromosomal aberrations, which must always be considered in the differential diagnosis, the most common being the 45,X/46,XY syndrome (see Chapter 586.1). It may be necessary to karyotype several tissues to establish mosaicism. Other complex genetic syndromes, many resulting from single gene mutations, are associated with varying degrees of ambiguity of the genitalia, particularly in the male. These entities must be identified on the basis of the associated extragenital malformations.

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by mutations in the sterol Δ7-reductase gene located on chromosome 11q12-q13. It is characterized by prenatal and postnatal growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the 2nd-3rd toes, and severe cognitive impairment (see Chapter 86.3). Its incidence is 1 in 20,000 to 30,000 live births in populations of northern and central European origin; 70% are male. Genotypic males usually have genital ambiguity and, occasionally, partial sex reversal with female genital ambiguity or complete sex reversal with female external genitals. Müllerian duct derivatives are usually absent. Affected 46,XX patients have normal genitalia. Two types of Smith-Lemli-Opitz syndrome have been recognized. The classical form (type I) described earlier and the acrodyssgenital syndrome, which is usually lethal within 1 yr and is associated with severe malformations, postaxial polydactyly, and extremely abnormal external genitalia (type II). Pyloric stenosis is associated with Smith-Lemli-Opitz syndrome type I and Hirschsprung disease with type II. Cleft palate, skeletal abnormalities, and 1 case of a lipoma of the pituitary gland have been seen in type II cases. Some authors believe in a spectrum of disease severity rather than in the above classification. Low plasma cholesterol with elevated 7-dehydrocholesterol, its precursor, are found in types I and II, and the levels do not correlate with severity. Maternal apolipoprotein E values do seem to correlate with severity. The most common prenatal expression of Smith-Lemli-Opitz syndrome is intrauterine growth retardation (see Chapter 86.3 for treatment).

46,XY DSD subjects also have been described in siblings with the α-thalassemia/mental retardation syndrome.

Bibliography is available at Expert Consult.

588.3 Ovotesticular DSD

Patricia A. Donohue

In ovotesticular DSD, both ovarian and testicular tissues are present, either in the same or in opposite gonads. Affected patients have ambiguous genitalia, varying from normal female with only slight enlargement of the clitoris to almost normal male external genitalia (see Fig. 588-2A).

Approximately 70% of all patients have a 46,XX karyotype. Ninety-seven percent of affected patients of African descent are 46,XX. Fewer than 10% of persons with ovotesticular DSD are 46,XY. Approximately 20% have 46,XX/46,XY mosaicism. Half of these are derived from more than 1 zygote and are chimeras (chi 46,XX/46,XY). The presence of paternal and both maternal alleles for some blood groups is demonstrated. An ovotesticular DSD chimera, 46,XX/46,XY, was reported as resulting from embryo amalgamation after in vitro fertilization. Each embryo was derived from an independent, separately fertilized ovum.

Examination of 46,XX ovotesticular DSD patients with Y-specific probes has detected fewer than 10% with a portion of the Y chromosome including the SRY gene. Ovotesticular DSD is usually sporadic, but a number of siblings have been reported. The cause of most cases of ovotesticular DSD is unknown.

The most frequently encountered gonad in ovotesticular DSD is an ovotestis, which may be bilateral. If unilateral, the contralateral gonad
Bibliography


is usually an ovary but may be a testis. The ovarian tissue is normal, but the testicular tissue is dysgenetic. The presence and function of testicular tissue can be determined by measuring basal and hCG-stimulated testosterone levels as well as AMH levels. Patients who are highly virilized and have had adequate testicular function with no uterus are usually reared as males. If a uterus exists, virilization is often mild and testicular function minimal; assignment of female sex may be indicated. Selective removal of gonadal tissue inconsistent with sex of rearing may be indicated. In a few families, 46,XY ovotesticular DSD subjects and 44,XX males have been described in the same sibship.

Defects in R-Spondin1, encoded by the RSPO1 gene, have been described in 46,XX ovotesticular DSD.

Pregnancies with living offspring have been reported in 46,XX ovotesticular DSD individuals reared as females, but very few males with ovotesticular DSD have fathered children. Approximately 5% of patients will develop gonadoblastomas, dysgerminomas, or seminomas.

**DIAGNOSIS AND MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT**

In the neonate, ambiguity of the genitals requires immediate attention to decide on the sex of rearing as early in life as possible. The family of the infant needs to be informed of the child's condition as early, completely, compassionately, and honestly as possible. Caution must be used to avoid feelings of guilt, shame, and discomfort. Guidance needs to be provided to alleviate both short-term and long-term concerns and to allow the child to grow up in a completely supportive environment. The initial care is best provided by a team of professionals that include neonatologists and pediatric specialists, endocrinologists, radiologists, urologists, psychologists, and geneticists, all of whom remain focused foremost on the needs of the child. Management of the potential psychologic upheaval that these disorders can generate in the child or the family is of paramount importance and requires physicians and other healthcare professionals with sensitivity, training, and experience in this field.

While awaiting the results of chromosomal analysis, pelvic ultrasonography is indicated to determine the presence of a uterus and ovaries. Presence of a uterus and absence of palpable gonads usually suggests a virilized XX female. A search for the source of virilization should be undertaken; this includes studies of adrenal hormones to rule out varieties of congenital adrenal hyperplasia, and studies of androgens and estrogens occasionally may be necessary to rule out aromatase deficiency. Virilized XX females are generally (but not always) reared as females even when highly virilized.

The absence of a uterus, with or without palpable gonads, often indicates an undervirilized male and an XY karyotype. Measurements of levels of gonadotropins, testosterone, AMH, and DHT are necessary to determine whether testicular production of androgen is present and is normal. Undervirilized males who are totally feminized may be reared as females. Certain significantly feminized infants, such as those with 5α-reductase deficiency, may be reared as males because these children virilize normally at puberty. Sixty percent of individuals with 5α-reductase deficiency assigned as female in infancy live as males as adults. An infant with a comparable degree of feminization resulting from an androgen receptor defect, such as CAIS, is best reared as a female.

When receptor disorders are suspected in the XY male with a small phallus (micro penis), a course of 3 monthly intramuscular injections of testosterone enanthate (25-50 mg) may assist in the differential diagnosis of androgen insensitivity, as well as in treatment.

In some mammals, the female exposed to androgens prenatally or in early postnatal life exhibits nontraditional sexual behavior in adult life. Most, but not all, girls who have undergone fetal masculinization from congenital adrenal hyperplasia or from maternal progestin therapy have female sexual identity, although during childhood they may appear to prefer male playmates and activities over female playmates and feminine play with dolls in mothering roles.

In the past it was thought that surgical treatment of ambiguous genitalia to create a female appearance, particularly when a vagina is present, was more successful than construction of male genitalia. Considerable controversy exists regarding these decisions. Sexual functioning is to a large extent more dependent on neurohormonal and behavioral factors than the physical appearance and functional ability of the genitalia. Similarly, controversy exists regarding the timing of the performance of invasive and definitive procedures, such as surgery. Whenever possible without endangering the physical or psychologic health of the child, an expert multidisciplinary team should consider deferring elective surgical repairs and gonadectomies until the child can participate in the informed consent for the procedure. One study of children (n = 59 boys and 18 girls) with gender dysphoria but without documentation of genomic or enzymologic abnormalities indicated that most of these children no longer have gender dysphoria after completion of puberty. Among those who do, homosexuality and bisexuality are the most frequent diagnoses.

For patients with DSD who have Y-chromosome material and intraabdominal gonads, gonadectomy is generally recommended because of the risk of gonadal tumors, many of which are malignant.

The pediatrician, pediatric endocrinologist, and psychologist, along with the appropriate additional specialists, should provide ongoing compassionate, supportive care to the patient and the patient's family throughout childhood, adolescence, and adulthood. Support groups are available for families and patients with many of the conditions discussed.

*Bibliography is available at Expert Consult.*
Bibliography

Diabetes mellitus (DM) is a common, chronic, metabolic disease characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are differentiated by insulin deficiency vs insulin resistance: type 1 diabetes mellitus (T1DM) results from deficiency of insulin secretion because of pancreatic β-cell damage; type 2 diabetes mellitus (T2DM) is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment. T1DM is the most common endocrine-metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Individuals with T1DM confront serious lifestyle alterations, including an absolute daily requirement for exogenous insulin, the need to monitor their own glucose level, and the need to pay attention to dietary intake. Morbidity and mortality stem from a constant potential for acute metabolic derangements and from long-term complications (usually in adulthood) that affect small and large blood vessels resulting in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities. The acute clinical manifestations are caused by hypoinsulinemic hyperglycemic ketoacidosis; the genesis of T1DM owes to autoimmune mechanisms; and the long-term complications are related to metabolic disturbances (hyperglycemia).
DM is not a single entity but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance. Table 589-1 presents a classification of diabetes and other categories of glucose intolerance. Three major forms of diabetes and several forms of carbohydrate intolerance are identified.

### TYPE 1 DIABETES MELLITUS

Formerly called insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes, T1DM is characterized by low or absent levels of endogenously produced insulin and by dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of T1DM. The natural history includes 4 distinct stages: (1) preclinical β-cell autoimmunity with progressive defect of insulin secretion, (2) onset of clinical diabetes, (3) transient remission “honeymoon period,” and (4) established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy. The onset occurs predominantly in childhood, with a median age of 7-15 yr, but it may present at any age. The incidence of T1DM has steadily increased in nearly all parts of the world (Fig. 589-1). T1DM is characterized by autoimmune destruction of pancreatic islet β cells. Both genetic susceptibility and environmental factors contribute to the pathogenesis. Susceptibility to T1DM is genetically controlled by alleles of the major histocompatibility complex class II genes expressing human leukocyte antigens (HLAs). Autoantibodies to β-cell antigens such as islet cell cytoplasm (ICA), insulin autoantibody (IAA), and antibodies to glutamic acid decarboxylase, ICA512 are detected in serum from affected subjects. These can be detected months to years before the onset of diabetes. Autoantibodies to glutamic acid decarboxylase, ICA512 are detected in serum from affected subjects. These can be detected months to years before the onset of diabetes. In some children and adolescents with apparent T1DM, the β-cell destruction is not immune mediated. This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β-cell destruction such as drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and insulin fibrosis.

### Table 589-1 Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
   A. Typical
   B. Atypical

III. Genetic defects of β-cell function
   A. MODY (maturity-onset diabetes of the young) syndromes
      1. MODY 1 chromosome 20, HNF4α
      2. MODY 2 chromosome 7, glucokinase
      3. MODY 3 chromosome 12, HNF1α, TCF-1
      4. MODY 4 chromosome 13, IPF-1
      5. MODY 5 chromosome 17, HNF1β, TCF-2
      6. MODY 6 chromosome 2q32, neuro-D-β2
   B. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearn-Sayre, diabetes melitus, deafness)
   C. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness); WFS1-Wolframin—chromosome 4p
      1. Wolfram locus 1—chromosome 4q22-24
      2. Wolfram mitochondrial
   D. Thiamine responsive megaloblastic anemia and diabetes

IV. Drug or chemical induced
   A. Antirejection—cyclosporine, sirolimus
   B. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)

C. L-Asparaginase
   D. β-Adrenergic blockers
   E. Vacor (rodenticide)
   F. Phenytoin (Dilantin)
   G. α-Interferon
   H. Diazoxide
   I. Nicotinic acid
   J. Pentamidine

V. Diseases of exocrine pancreas
   A. Cystic fibrosis-related diabetes
   B. Trauma—pancreatectomy
   C. Pancreatitis—ionizing radiation
   D. Others

VI. Infections
   A. Congenital rubella
   B. Cytomegalovirus
   C. Hemolytic-uremic syndrome

VII. Variants of type 2 diabetes
   A. Genetic defects of insulin action
      1. Rabson-Mendenhall syndrome
      2. Leprechaunism
      3. Lipoatrophic diabetes syndromes
      4. Type A insulin resistance—acanthosis
   B. Acquired defects of insulin action
      1. Endocrine tumors—rare in childhood
      C. Pheochromocytoma
      D. Cushing
      E. Others
      1. Antiinsulin receptor antibodies

VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency
   A. Prader-Willi syndrome, chromosome 15
   B. Down syndrome, chromosome 21
   C. Turner syndrome
   D. Klinefelter syndrome
   E. Others
      1. Bardet-Biedel
      2. Alstrom
      3. Werner
      F. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
      G. Celiac disease
      H. Autoimmune polyendocrinopathy

IX. Gestational diabetes
   A. Transient—chromosome 6q24, KCNJ11, ABCC8, INS, HNF1β, others
   B. Permanent—ageneisis of pancreas—glucokinase deficiency, homozygous, KCNJ11, ABCC8, others

resistance and often a progressive defect in insulin secretion. This type of diabetes was formerly known as adult-onset diabetes mellitus or non-insulin-dependent diabetes mellitus.

The presentation of T2DM is typically more insidious than that with T1DM. In contrast to patients with T1DM who are usually ill at the time of diagnosis and whose presentation rarely spans more than a few weeks, children with T2DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or the incidental finding of glycosuria during routine physical examination. A history of polyuria and polydipsia is not always a cardinal clinical feature in these patients. The incidence of T2DM in children has increased by more than 10-fold, depending on geography and mostly as a result of the epidemic of childhood obesity (see Chapter 47). Pediatric T2DM may account for as many as 80% of the new cases of diabetes, especially in obese African-American and Mexican-American adolescents. Acanthosis nigricans (dark pigmentation of skin creases in the nape of the neck especially), a sign of insulin resistance, is present in the majority of patients with T2DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis (see Chapter 652). However, the serum insulin elevation is usually disproportionately lower than that of age-, weight-, and sex-matched nondiabetic children and adolescents, suggesting a state of insulin insufficiency. In some individuals, it may represent slowly evolving T1DM.

In some children with a strong family history of diabetes, impaired glucose tolerance (IGT) may occur in a pattern implying dominant inheritance. This pattern of diabetes has been termed maturity-onset diabetes of the young (MODY): it may require insulin treatment, can be treated with sulfonylureas with varying degrees of success, and is often now referred to as monogenic diabetes. MODY may present with fasting glucose concentration of 99 mg/dL (6.9 mmol/L) is the upper limit of “normal.” This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications.

In the absence of pregnancy, IGT is not a clinical entity but rather a risk factor for future diabetes and cardiovascular disease. This may be observed as an intermediate stage in any of the disease processes listed in Table 589-1. IGT is often associated with the insulin receptors, Rad (Ras associated with diabetes), and possibly apolipoprotein C-III. A recent metaanalysis suggests that the incidence of T2DM has a complexly inverse relationship with birthweight in some populations, depending on ethnic and genetic factors.

**OTHER SPECIFIC TYPES OF SECONDARY DIABETES**

Examples include diabetes secondary to exocrine pancreatic diseases (cystic fibrosis), other endocrine diseases (Cushing syndrome), and ingestion of certain drugs or poisons (the rodenticide Vacor). In organ transplantation survivors, there is a linkage between cyclosporine and tacrolimus and posttransplantation DM, ascribed to a number of mechanisms. Certain genetic syndromes, including those with abnormalities of the insulin receptor, also are included in this category. There are no associations with HLA types, autoimmunity, or islet cell antibodies among the entities in this subdivision.

Table 589-2 details the current criteria for the diagnosis of type 1 and type 2 DM. It should be noted that a fasting blood glucose that exceeds 125 mg/dL (6.9 mmol/L) is the accepted criterion for the diagnosis of diabetes.

**IMPAIRED GLUCOSE TOLERANCE**

The term impaired glucose tolerance (IGT) refers to a metabolic stage that is intermediate between normal glucose homeostasis and diabetes. A fasting glucose concentration of 99 mg/dL (5.5 mmol/L) is the upper limit of “normal.” This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications.

Many individuals with IGT (fasting glucose 100-125 mg/dL) are euglycemic in their daily lives and may have normal or nearly normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test.

Figure 589-1 Incidence of type 1 diabetes in children ages 0-14 yr, by geographical region and over time. A, Estimated global incidence of type 1 diabetes, by region, in 2011. B, Time-based trends for the incidence of type 1 diabetes in children ages 0-14 yr in areas with high or high-intermediate rates of disease. (From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes. Lancet 383:69–78, 2014, Fig. 1, p. 70.)
Diabetes Type 2763

Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus

<table>
<thead>
<tr>
<th>IMPAIRED GLUCOSE TOLERANCE</th>
<th>DIABETES MELLITUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose 100-125 mg/dL (5.6-7.0 mmol/L)</td>
<td>Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L) or 2-hr plasma glucose during the OGTT ≥140 mg/dL but &lt;200 mg/dL (11.1 mmol/L) or Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2 hr plasma glucose during the OGTT ≥200 mg/dL or Hemoglobin A1C ≥6.5%†</td>
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*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.

†Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.


resistance syndrome (also known as syndrome X or metabolic syndrome), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both, and hypertension (see Chapter 47). Insulin resistance is directly involved in the pathogenesis of T2DM. IGT appears as a risk marker for this type of diabetes at least in part because of its correlation with insulin resistance. Table 589-2 presents the diagnostic criteria for IGT.

589.2 Type 1 Diabetes Mellitus (Immune Mediated)

Britta M. Svoren and Nicholas Jospe

Epidemiology

T1DM accounts for approximately 10% of all cases of diabetes, affecting up to 3 million people in the United States and more than 15 million people in the world. Using population-based estimates of diabetes incidence and prevalence, a recent study indicates that approximately 15,000 youths are diagnosed with type 1 diabetes each year. While it accounts for most cases of diabetes in childhood, it is not limited to this age group; new cases occur to continue in adult life and approximately 50% of individuals with T1DM present as adults. The incidence of T1DM is highly variable among different ethnic groups (see Fig. 589-1). The overall age-adjusted incidence of T1 DM varies from 0.7 in 100,000 per yr in Karachi (Pakistan) to more than 40 in 100,000 per yr in Finland. The incidence of T1DM is increasing in most (but not all) populations and this increase appears to be most marked in populations where the incidence of autoimmune diseases was historically low. Data from Western European diabetes centers suggest that the annual rate of increase in T1DM incidence is 2-5%, whereas some central and eastern European countries demonstrate an even more rapid increase—up to 9%. The rate of increase is greatest among the youngest children. In the United States, the overall prevalence of diabetes among school-age children is approximately 1.9 in 1,000, increasing from a prevalence of 1 in 1,430 children at 5 yr of age to 1 in 360 children at 16 yr of age. Among African-Americans, the occurrence of T1DM is 30-60% of that seen in American whites. The annual incidence of new cases in the United States is now approximately 19.7 in 100,000 among youth younger than 10 yr and 18.6 in 100,000 of those older than 10 yr. It is estimated that 30,000 new cases occur each year in the United States, affecting 1 in 300 children and as many as 1 in 100 adults during the life span. Rates are similar or higher in most Western European countries and significantly lower in Asia and Africa.

Girls and boys are almost equally affected, but there is a modest female preponderance in some low-risk populations (e.g., the Japanese); there is no apparent correlation with socioeconomic status. Peaks of presentation occur in 2 age groups: at 5-7 yr of age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the second peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin). The understanding of the cause of diabetes or of its increased incidence remains elusive. A growing number of cases are presenting between 1 and 2 yr of age, especially in high-risk groups; the average age of presentation is older in low-risk populations. Low-risk groups that migrate to a high-risk country seem to acquire the increased risk of that country. On the other hand, there can be marked differences in incidence rates in various ethnic groups within the same country; for example, incidence rates in the 10-14 yr age group in the United States range from a low of 7.1 in Native Americans, to 17.6 in Hispanics, 19.2 in African-Americans, and 32.9 in whites. These variations also remain unexplained at this time.

Genetics

There is a clear familial clustering of T1DM, with prevalence in siblings approaching 6%, whereas the prevalence in the general population in the United States is only 0.4%. Risk of diabetes is also increased when a parent has diabetes and this risk differs between the 2 parents; the risk is 3-4% if the mother has diabetes but 5-6% when the father has diabetes. In monozygotic twins, the concordance rate ranges from 30-65%, whereas dizygotic twins have a concordance rate of 6-10%. Because the concordance rate of dizygotic twins is higher than the sibling risk, factors other than the shared phenotypes (e.g., the shared intrauterine environment) may play a role in increasing the risk in dizygotic twins. Furthermore, the genetic susceptibility for T1DM in the parents of a child with diabetes is estimated at 3%. It should be kept in mind that although there is a large genetic component in T1DM, 85% of newly diagnosed type 1 diabetic patients do not have a family member with T1DM. Thus, we cannot rely on family history to identify patients who may be at risk for the future development of T1DM as most cases will develop in individuals with no such family history.

Monogenic Type 1 Diabetes Mellitus

Classic single-gene defects are an extremely rare cause of type 1 diabetes, and more than 20 genes have been linked to monogenic diabetes, in children and in adults. In 2 rare syndromes (IPEX and APS-1) the genetic susceptibility that leads to diabetes is caused by a classic single-gene defect. The IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome is caused by mutations of the FOXP3 and other genes. The FOXP3 (forkhead box P3) is a gene involved in immune system responses. A member of the FOX family protein, FOXP3 appears to function as the master regulator in the development and function of regulatory T cells. These mutations lead to the lack of a major population of regulatory T lymphocytes with resulting overwhelming autoimmunity and development of diabetes (as early as 2 days of age) in approximately 90% of the children with this disorder.

APS-1 (autoimmune polyendocrinopathy syndrome type 1) is caused by mutations of the AIRE (autoimmune regulator) gene, leading to abnormalities in expression of peripheral antigens within the thymus and/or abnormalities of negative selection in the thymus. This results in widespread autoimmunity. Approximately 18% of children with this syndrome develop type 1 diabetes.

Genes Altering the Risk of Autoimmune Type 1 Diabetes Mellitus

For most patients with T1DM, their risk of developing T1DM is modified by the influence of several risk loci. The genomic region with by
far the greatest contribution to the risk of T1DM is the major histocompatibility complex on chromosome 6. The region with the next highest odds ratio is the promoter region 5′ of the insulin gene on chromosome 11. Studies have identified more than 50 other risk loci. These loci include insulin (INS), protein tyrosine phosphatase nonreceptor type 2 (PTPN22), protein tyrosine phosphatase nonreceptor type 2 (PTPN2), interleukin (IL)-2 receptor (CD25), a lectin-like gene (KIAA0350), v-erb-b2 erythroblastic leukemia viral oncogene homolog 3e (ERBB3e), cytotoxic T-lymphocyte antigen 4 (CTLA4), and interferon-induced with helicase C domain 1 (IFIH1). However, except for PTPN22, their contribution is relatively small, thus making them less useful for predicting the genetic risk of T1DM in a given individual. On balance, the known functions of these genes suggest the primary etiologic pathways of diabetes, namely, HLA class II and class I molecules binding, T and B cell activation, innate pathogen viral responses, chemokine and cytokine signaling, and T regulatory and antigen-presenting cell functions.

**Major Histocompatibility Complex/Human Leukocyte Antigen Encoded Susceptibility to Type 1 Diabetes Mellitus**

The major histocompatibility complex is a large genomic region that contains a number of genes related to immune system function in humans. These genes are further divided into HLA classes I, II, III, and IV genes. Class II genes are the ones most strongly associated with risk of T1DM, but some of the risk associated with various HLA types is a result of variation in genes in HLA classes other than class II. Overall, genetic variation in the HLA region can explain 40-50% of the genetic risk of T1DM (Fig. 589-2).

Some of the known associations include the HLA DR3/4-DQ2/8 genotype; compared to a population prevalence of T1DM of approximately 1 in 300, DR3/4-DQ2/8 newborns from the general population have a 1 in 20 genetic risk. This risk of development of T1DM is even higher when the high-risk HLA haplotypes are shared with a sibling or parent with T1DM. Thus, if a sibling has T1DM and shares the same high-risk DR3/4-DQ2/8 haplotype with another sibling, then the risk of autoimmunity in the other sibling is 50%. And this risk approaches 80% when siblings share both HLA haplotypes identical by descent. This is known as the relative paradox and points to the existence of other shared genetic risk factors (most likely in the extended HLA haplotype).

With advances in genotyping, further discrimination is possible and we can identify more specific risk ratios for specific haplotypes. For example, the DRB1*0401-DQA1*0301-DQB1*0302 haplotype has an odds ratio (OR) of 8.39 whereas the DRB1*0401-DQA1*0301-DQB1*0201 has an OR of 0.35, implicating the DQB1*0302 allele as a dramatically protective DR-DQ haplotype (e.g., DRB1*1501-DQA1*0102-DQB1*0602 [OR = 0.03], DRB1*1401-DQA1*0101-DQB1*0503 [OR = 0.02], and DRB1*0701-DQA1*0201-DQB1*0303 [OR = 0.02]). The DR2 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) is dominantly protective and is present in 20% of the general population but is seen in only 1% of patients with T1DM.

**Role of Aspartate at Position 57 in DQB1**

DQB1*0302 (high risk for diabetes) differs from DQB1*0201 (protective against diabetes) only at position 57, where it lacks an aspartic acid residue. The DQB1*0201 allele (increased risk for diabetes) also lacks aspartic acid at position 57, and it has been proposed that the presence of aspartate at this position alters the protein recognition and protein binding characteristics of this molecule. Although the absence of aspartate at this position appears to be important in most studies on white individuals, it does not have the same role in Korean and Japanese populations. Moreover, certain low-risk DQB1 genotypes also lack aspartic acid at position 57, including DQB1*0302/DQB1*0201 (DR7) and DQB1*0201 (DR3)/DQB1*0201 (DR7). Thus, the presence of aspartate at this position is usually, but not always, protective in white populations but not necessarily in other populations.

**Role of Human Leukocyte Antigen Class I**

Although the alleles of class II HLA genes appear to have the strongest associations with diabetes, recent genotyping studies and analyses of pooled data have identified associations with other elements in the HLA complex, especially HLA-A and HLA-B. The most significant association is with HLA-B39, which confers high risk for T1DM in 3 different populations, makes up the majority of the signal from HLA-B, and is associated with a lower age of onset of the disease.

**Insulin Gene Locus, IDDM2**

The second locus found to be associated with risk of T1DM was labeled IDDM2 and has been localized to a region upstream of the insulin gene (i.e., 5′ of the insulin gene). It is estimated that this locus accounts for approximately 10% of the familial risk of T1DM. Susceptibility in this region has been primarily mapped to a variable number of tandem repeats approximately 500 bp upstream of the insulin gene. This highly polymorphic region consists of anywhere from 30 to several hundred repeats of a 14-15 bp unit sequence (ACAGGGGCTCGGGG). A shorter number of repeats is associated with increased risk of T1DM.

**PTPN22 (Lymphoid Tyrosine Phosphatase)**

A single-nucleotide polymorphism in the PTPN22 gene on chromosome 1p13 that encodes lymphoid tyrosine phosphatase correlates strongly with the incidence of T1DM in 2 independent populations. This gene has an association with several other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, vitiligo, and Graves disease.

**Cytotoxic T Lymphocyte Antigen 4**

The cytotoxic T lymphocyte antigen 4 (CTLA-4) gene is located on chromosome 2q33 and is associated with T1DM as well as Graves disease, Hashimoto thyroiditis, celiac disease, and systemic lupus erythematosus. This gene is a negative regulator of T-cell activation.

**Interleukin-2 Receptor**

Single-nucleotide polymorphisms in or near the gene for the IL-2 receptor have been found to have an association with T1DM risk. Studies with IL-2 in T1DM to date have not been successful in halting progression.

**Interleukin-1 Receptor**

IL-1 receptor activation and chemokines involved in monocyte/macrophage and neutrophil chemotaxis have been also identified as critical steps in nitric oxide–induced islet necrosis and subsequent apoptosis. Indeed, inhibition of the activation of IL-1β–dependent inflammatory pathways by an IL-1 receptor antagonist in cultured rat islets exposed to nitric oxide prevented necrosis and apoptosis.
supporting evaluation in human islets in vitro and potentially as a posttransplantation therapy. IL-1 blockade in patients with T1DM has not halted progression.

**Interferon-Induced Helicase**
Another gene identified as having a modest effect on the risk of T1DM is the interferon-induced helicase (IFIH1) gene. Significant association exists with T1DM as well as Graves disease and multiple sclerosis. This gene is thought to play a role in protecting the host from viral infections and given the specificity of different helicases for different RNA viruses, it is possible that knowledge of this gene locus will help to narrow down the list of viral pathogens that may have a role in T1DM.

**ENVIRONMENTAL FACTORS**
That 50% or so of monozygotic twins are discordant for T1DM, the variation seen in urban and rural areas populated by the same ethnic group, the change in incidence that occurs with migration, the increase in incidence that has been seen in almost all populations in the last few decades, and the occurrence of seasonality all provide evidence that environmental factors also play a significant role in the causation of T1DM.

**Viral Infections**
It is possible that various viruses do play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism, stands out in the environmental etiology of T1DM. Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts. Invoked mechanisms involved direct infection of β cells by viruses resulting in lysis and release of self-antigens, direct viral infection of antigen-presenting cells causing increased expression of cytokines, and “molecular mimicry,” the notion that viral antigens exhibit homology to self-epitopes.

**Congenital Rubella Syndrome**
The clearest evidence of a role for viral infection in human T1DM is seen in congenital rubella syndrome. Prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children. The time lag between infection and development of diabetes may be as high as 20 yr. T1DM after congenital rubella is more likely in patients that carry the higher-risk genotypes. Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth or when live-virus rubella immunization is used.

**Enteroviruses**
Studies show an increase in evidence of enteroviral infection in patients with T1DM and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently develop T1DM. In addition, there are case reports of association between enteroviral infection and subsequent T1DM. But the true significance of these infections remains unknown at this time.

**Mumps Virus**
It has been variably observed that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM in some cases. Although mumps may play a role in some cases of diabetes, the fact that T1DM diabetes incidence has increased steadily in several countries after universal mumps vaccination was introduced and that the incidence is extremely low in several populations where mumps is still prevalent indicates that mumps alone is not a major causal factor in diabetes.

**The Hygiene Hypothesis: Possible Protective Role of Infections**
Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes. The hygiene hypothesis states that T1DM is a disease of industrialized countries, where the observation that there are fewer infections implies that the immune system is less well trained for its main task, namely host defense. Some call this theory the “microbial deprivation hypothesis.” The hygiene hypothesis states that lack of exposure to childhood infections may increase an individual’s chances of developing autoimmune diseases, including T1DM. Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed. The incidence of T1DM differs almost 6-fold between Russian Karelia and Finland, even though both are populated by a genetically related population and are adjacent to each other and at the same latitude. The incidence of autoimmunity in the 2 populations varies inversely with immunoglobulin (Ig) E antibody levels, and IgE is involved in the response to parasitic infestation. All these observations indicate that decreased exposure to certain parasites and other microbes in early childhood may lead to an increased risk of autoimmunity in later life, including autoimmune diabetes. On the other hand, retrospective case-control studies have been equivocal at best and direct evidence of protection by childhood infections is still lacking.

**Diet**
Breastfeeding may lower the risk of T1DM, either directly or by delaying exposure to cow’s milk protein. Early introduction of cow’s milk protein and early exposure to gluten are implicated in the development of autoimmunity and it has been suggested that this is a result of the “leakiness” of the immature gut to protein antigens. Implicated antigens include β-lactoglobulin, a major lipocalin protein in bovine milk, which is homologous to the human protein glycodelin (PP14), a T-cell modulator. Other studies focused on bovine serum albumin as the inciting antigen, but the data are contradictory and not yet conclusive. In addition, milk and milk products are also indicators of the level of contamination of persistent organic pollutants, polychlorinated biphenyls, dioxin, and others. One large study in infants who are at high risk for T1DM did not demonstrate a reduced incidence of diabetes-associated autoantibodies when fed an extensively hydrolyzed vs cow milk–based formula. A smaller study demonstrated a reduced incidence of autoantibody production in infants fed a whey-based formula that was free of bovine insulin. Additional studies are underway and should be available in 2017.

Other dietary factors that have been suggested at various times as playing a role in diabetes risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), deficiency is more common in northern countries like Finland, and there is some epidemiologic evidence that decreased vitamin D levels in pregnancy or early childhood may be associated with diabetes risk; but the evidence is not yet conclusive and it is hoped that ongoing studies like TEDDY (The Environmental Determinants of Diabetes in the Young) will help to resolve some of the uncertainties in this area.

**Psychologic Stress**
Several studies show an increased prevalence of stressful psychologic situations among children who subsequently developed T1DM. Whether these stresses only aggravate preexisting autoimmunity or whether they can actually trigger autoimmunity through epigenetic mechanisms remains unknown.

**PATHOGENESIS AND NATURAL HISTORY OF TYPE 1 DIABETES MELLITUS**
In T1DM, a genetically susceptible host develops autoimmunity against the host’s own β cells. What triggers this autoimmune response remains unclear at this time. In some (but not all) patients, this autoimmune process results in progressive destruction of β cells until a critical mass
of β cells is lost and insulin deficiency develops. Insulin deficiency, in turn, leads to the onset of clinical signs and symptoms of T1DM. At the time of diagnosis, some viable β cells are still present and these may produce enough insulin to lead to a partial remission of the disease (honeymoon period) but over time, almost all β cells are destroyed and the patient becomes totally dependent on exogenous insulin for survival (Fig. 589-3). Over time, some of these patients develop secondary complications of diabetes that appear to be related to how well-controlled the diabetes has been. Thus, the natural history of T1DM involves some or all of the following stages:

**Initiation of Autoimmunity**

Genetic susceptibility to T1DM is determined by several genes (see “Genetics” below), with the largest contribution coming from variants in the HLA system. But it is important to keep in mind that even with the highest-risk haplotypes, most carriers will not develop T1DM. Even in monozygotic twins, the concordance is 30-65%. The observed rise in incidence of T1DM within an essentially genetically stable patient population implies that something has accordingly changed in the environment or the way children are raised. A number of factors, including prenatal influences, diet in infancy, viral infections, lack of exposure to certain infections, even psychologic stress, are implicated in the pathogenesis of T1DM, but their exact role and the mechanism by which they trigger or aggravate autoimmunity remains uncertain (Fig. 589-4). What is clear is that markers of autoimmunity are much more prevalent than clinical T1DM, indicating that initiation of autoimmunity is a necessary but not a sufficient condition for T1DM.

Whatever the triggering factor, it seems that in most cases of T1DM that are diagnosed in childhood, the onset of autoimmunity occurs very early in life. In a majority of the children diagnosed before age 10 yr, the first signs of autoimmunity appear before age 2 yr. Development of autoimmunity is associated with the appearance of several autoantibodies. IAAs are usually the first to appear in young children, followed by glutamic acid decarboxylase 65 kDa, and later by tyrosine phosphatase insulinoma–associated 2 and zinc transporter 8 antibodies. The earliest antibodies are predominantly of the IgG subclass. Not only is there “spreading” of autoimmunity to more antigens (IAA, and...
then glutamic acid decarboxylase 65 and insulinoma-associated 2 and zinc transporter 8) but there is also epitope spreading within 1 antigen. Initial glutamic acid decarboxylase 65 antibodies tend to be against the middle region or the carboxyl-terminal region, whereas aminoterminal antibodies usually appear later and are less common in children.

**Preclinical Autoimmunity with Progressive Loss of β-Cell Function**

In some, but not all, patients, the appearance of autoimmunity is followed by progressive destruction of β cells. Antibodies are a marker for the presence of autoimmunity, but the actual damage to the β cells is primarily T-cell mediated (Fig. 589-5). Histologic analysis of the pancreas from patients with recent-onset T1DM reveals insulitis, with an infiltration of the islets of Langerhans by mononuclear cells, including T and B lymphocytes, monocytes/macrophages, and natural killer cells. In the nonobese diabetic mouse, a similar cellular infiltrate is followed by linear loss of β cells until they completely disappear. But it appears that the process in human T1DM is not necessarily linear and there may be an undulating downhill course, with remissions and relapses, in the development of T1DM.

**Role of Autoantibodies**

Even though T1DM does not occur as a direct consequence of autoantibody formation, the risk of developing clinical disease increases dramatically with an increase in the number of antibodies; only 30% of children with 1 antibody will progress to diabetes, but this risk increases to 70% when 2 antibodies are present and 90% when 3 are present. The risk of progression also varies with the intensity of the antibody response and those with higher antibody titers are more likely to progress to clinical disease. Another factor that appears to influence progression of β-cell damage is the age at which autoimmunity develops; children in whom IAAs appeared within the 1st 2 yr of life rapidly developed anti-islet cell antibodies and progressed to diabetes more frequently than children in whom the first antibodies appeared between ages 5 and 8 yr.

**Role of Genetics in Disease Progression**

Genetics plays a role in progression to clinical disease. In a large study of healthy children, the appearance of single antibodies is relatively common and usually transient, and does not correlate with the presence of high-risk HLA alleles, but those carrying high-risk HLA alleles are more likely to develop multiple antibodies and progress to disease. Similarly, the appearance of antibodies is more likely to predict diabetes in those with a family history of diabetes vs those with no family history of T1DM. Thus, it may be the case that environmental factors can induce transient autoimmunity in many children, but those with genetic susceptibility are more likely to see progression of autoimmunity and eventual development of diabetes.

**Role of Environmental Factors**

In addition to genetic factors, environmental factors may also act as accelerators of T1DM after the initial appearance of autoimmunity. This is evident from the fact that the incidence of T1DM can vary several-fold between populations that have the same prevalence of autoimmunity. For instance, the incidence of T1DM in Finland is almost 4-fold higher than in Lithuania, but the incidence of autoimmunity is similar in both countries.

The fact that all children with evidence of autoimmunity and of autoreactive T cells do not progress to diabetes indicates that there are “checkpoints” at which the autoimmune process can be halted or

![Figure 589-5](image-url)  
**Figure 589-5** Schematic of the autoimmune response against pancreatic β cells. An insult to the pancreas leads to the release of β-cell antigens (GAD65), which are taken up by antigen-presenting cells (APCs) and the epitopes presented to the CD4 T cells. Type and stage of activation of APCs as well as the cytokine environment, in which the CD4 T-cell priming takes place, dictate the differentiation of autoreactive T cells toward diabetogenic T-helper type 1 (Th1) cells, T-helper type 2 (Th2) cells, or antigen-specific regulatory T cells. A predominant Th1 autoimmune response results in the recruitment and differentiation of cytotoxic CD8 cells, which attack the pancreatic β cells, leading to a massive release of β-cell antigens (Ag), epitope spreading, and destruction of the pancreatic islets. B, B lymphocyte; CTL, cytotoxic cell; DC, dendritic cell; IL, interleukin; INFγ, interferon-γ; M, macrophage; TGF-β, tumor growth factor β. (Adapted from Casares S, Brumeanu TD: Insights into the pathogenesis of T1DM: a hint for novel immunospecific therapies, Curr Mol Med 1:357–378, 2001.)
reversed before it progresses to full-blown diabetes. This has raised the possibility of preventing T1DM by intervening in the preclinical stage.

**Onset of Clinical Disease**

Patients with progressive β-cell destruction will eventually present with clinical T1DM. It was thought that 90% of the total β-cell mass is destroyed by the time clinical disease develops, but later studies have revealed that this is not always the case. It now appears that β-cell destruction is more rapid and more complete in younger children, while in older children and adults the proportion of surviving β cells is greater (10-20% in autopsy specimens) and some β cells (about 1% of the normal mass) survive up to 30 yr after the onset of diabetes. As autopsies are usually done on patients who died of diabetic ketoacidosis, these figures may underestimate the actual β-cell mass present at diagnosis. Functional studies indicate that up to 40% of the insulin secretory capacity may be preserved in adults at the time of presentation of T1DM. Ultrasonic assays indicate that C-peptide production is measurable decades after onset of T1DM. The fact that newly diagnosed diabetic individuals may still have a significant surviving β-cell mass is important because it raises the possibility of secondary prevention of T1DM. Similarly, the existence of viable β cells years or decades after initial presentation indicates that even patients with long-standing diabetes may be able to exhibit some recovery of β-cell function if the autoimmune destructive process can be halted and islet cell regeneration occurs.

**PREDICTION AND PREVENTION**

Autoimmunity precedes clinical T1DM, and indicators of maturing autoimmune responses may be useful markers for disease prediction. Individuals at risk for T1DM can be identified by a combination of genetic, immunologic, and metabolic markers. The most informative genetic locus, HLA class II, confers about half of the total genetic risk but has a low positive predictive value (PPV) when used in the general population. Autoantibodies provide a practical readout of β-cell autoimmunity, are easily sampled in venous blood, and have become the mainstay of T1DM prediction efforts. In the 1st-degree relatives of patients with T1DM, the number of positive autoantibodies can help estimate the risk of developing T1DM: low risk (single autoantibodies: PPV of 2-6%), moderate risk (2 autoantibodies: PPV of 21-40%), and high risk (>2 autoantibodies: PPV of 59-80%) over a 5 yr period. In children carrying the T1DM highest-risk genotype (HLA-DQB1*0201-DQA1*0501-DQB1*0302-DQA1*03), insulin is almost 10 times more frequent (PPV 21%) than in children with other genotypes (PPV 2.2%). But while autoantibodies are useful for the prediction of T1DM in the relatives of patients with T1DM, outside of that obvious population, the screening of the general population would be required in order to identify healthy subjects at risk of T1DM. Indeed, close to 2 of 10 individuals with new-onset T1DM have no family background of T1DM. This has been difficult, in part, because the observed autoantibody prevalence greatly exceeds the low disease prevalence in non-relatives, leading to high false-positive rates.

**Primary Prevention of Type 1 Diabetes Mellitus**

A safe, effective, inexpensive, and easily administered intervention could theoretically be targeted at all newborns, but no such universally effective intervention is yet available. Delaying the introduction of cow’s milk protein, delaying introduction of cereals, and increasing the duration of breastfeeding are all potentially beneficial but of unproven value.

In high-risk populations (relatives of individuals with T1DM, especially those with high-risk genotypes), it is feasible to test more targeted interventions. Parenteral insulin and nasal insulin proved similarly ineffective in preventing diabetes, but oral insulin appeared to delay the incidence of diabetes in only some of autoantibody-positive but still prediabetic patients. In the approach to the newly diagnosed patient with T1DM, antigen-specific immunotherapy trials studying the effect of glutamic acid decarboxylase formulated in aluminum hydroxide, IL-1β inhibition, or intranasal insulin have been negative, and anti-CD3 antibodies have been inconclusive.

**Secondary Prevention**

Immunosuppressants like cyclosporine have been tested after the onset of T1DM, but while they may prolong the honeymoon period, they are associated with significant side effects and are only effective as long as they are being administered, so their use for this purpose has been abandoned.

The possibility of using glucagon-like peptide (GLP)-1 agonists (e.g., exenatide) alone or in combination with immunomodulatory therapies is also being explored as these agents are capable of increasing β-cell mass in animals.

**PATHOPHYSIOLOGY**

Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use. Insulin levels must be lowered to then mobilize stored energy during the fasted state. Thus, in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue (Table 589-3). T1DM is a progressive low-insulin catabolic state in which feeding does not reverse, but rather exaggerates, these catabolic processes. With moderate insulinopenia, glucose utilization by muscle and fat decreases and postprandial hyperglycemia appears. At even lower insulin levels, the liver produces excessive glucose via gluconeogenesis and glucoseogenesis, and fasting hyperglycemia begins. Hyperglycemia produces an osmotic diuresis (glycosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L). The resulting loss of calories and electrolytes, as well as the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon). These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting glucoseogenesis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose utilization and glucose clearance (epinephrine, growth hormone, cortisol).

**Table 589-3 Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue***

<table>
<thead>
<tr>
<th>HIGH PLASMA INSULIN (POSTPRANDIAL STATE)</th>
<th>LOW PLASMA INSULIN (FASTED STATE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Glucose uptake</td>
</tr>
<tr>
<td>Glycogen synthesis</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Absence of gluconeogenesis</td>
<td>Gluconeogenesis</td>
</tr>
<tr>
<td>Lipogenesis</td>
<td>Absence of lipogenesis</td>
</tr>
<tr>
<td>Absence of ketogenesis</td>
<td>Ketogenesis</td>
</tr>
<tr>
<td>Muscle</td>
<td>Glucose uptake</td>
</tr>
<tr>
<td>Glucose oxidation</td>
<td>Fatty acid and ketone oxidation</td>
</tr>
<tr>
<td>Glycogen synthesis</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>Proteolysis and amino acid release</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Glucose uptake</td>
</tr>
<tr>
<td>Lipid synthesis</td>
<td>Lipolysis and fatty acid release</td>
</tr>
<tr>
<td>Triglyceride uptake</td>
<td>Absence of triglyceride uptake</td>
</tr>
</tbody>
</table>

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.
The combination of insulin deficiency and elevated plasma values of the counterregulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids. The hormonal interplay of insulin deficiency and glucagon excess shuts the free fatty acids into ketone body formation; the rate of formation of these ketone bodies, principally β-hydroxybutyrate and acetacetate, exceeds the capacity for peripheral utilization and renal excretion. Accumulation of these keto acids results in metabolic acidosis (diabetic ketoacidosis [DKA]) and compensatory rapid deep breathing in an attempt to excrete excess CO₂ (Kussmaul respiration). Acetone, formed by nonenzymatic conversion of acetacetate, is responsible for the characteristic fruity odor of the breath. Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte and bicarbonate regenerating ability. With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

**CLINICAL MANIFESTATIONS**

In diabetes the decreasing β-cell mass with worsening insulinopenia, progressive hyperglycemia, and eventual ketoacidosis all imply that symptoms steadily increase, from early intermittent polyuria to DKA and coma, over weeks usually, rather than months. Initially, when only insulin reserve is limited, occasional postprandial hyperglycemia occurs. When the serum glucose increases above the renal threshold, intermittent polyuria or nocturia begins. With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, often with nocturnal enuresis, and polydipsia becomes more apparent. Female patients may develop menilial vaginitis from the chronic glycosuria. Calories are lost in the urine (glycosuria), triggering a compensatory hyperphagia. If this hyperphagia does not keep pace with the glycosuria, loss of body fat ensues, with clinical weight loss and diminished neurocognitive function, and possible coma. Approxi-

**KETOACIDOSIS**

DKA is the end result of the metabolic abnormalities resulting from a severe deficiency of insulin or insulin effectiveness. The latter occurs during stress as counterregulatory hormones block insulin action. DKA occurs in 20–40% of children with new-onset diabetes and in children with known diabetes who omit insulin doses or who do not successfully manage an intercurrent illness. DKA may be arbitrarily classified as mild, moderate, or severe (Table 589-4), and the range of symptoms depends on the depth of ketoacidosis. There is a large amount of ketonuria, an increased ion gap, a decreased serum bicarbonate (or total CO₂) and pH, and an elevated effective serum osmolality, indicating hypertonic dehydration.

**TREATMENT**

Therapy is tailored to the degree of insulinopenia at presentation. Most children with new diabetes have mild to moderate symptoms, have minimal dehydration with no history of emesis, and have not progressed to ketoacidosis. Once DKA has resolved in the newly diagnosed child, therapy is transitioned to that described for children with known diabetes who develop DKA are usually transitioned to their previous insulin regimen.

**NEW-ONSET DIABETES WITHOUT KETOACIDOSIS**

Excellent diabetes control involves many goals: to maintain a balance between tight glucose control and avoiding hypoglycemia, to eliminate polyuria and nocturia, to prevent ketoacidosis, and to permit normal growth and development with minimal effect on lifestyle. Therapy...
encompasses initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishment of the life routines. Each aspect should be addressed early in the overall care.

### Insulin Therapy

Several factors influence the initial daily insulin dose per kilogram of body weight. The dose is usually higher in pubertal children. It is also higher in those who are in DKA at the time of presentation. Table 589-5 shows the recommended starting total daily dose (units/kg/day) of insulin in children.

The initial insulin schedule should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β cell. There are inherent limits to our ability to mimic the β cell. Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose; absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin release ceases and serum levels quickly lower with a normally rapid clearance. The absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation. Despite these fundamental physiologic differences, acceptable glucose control can be obtained with insulin analogs used in a basal-bolus regimen, that is, with slow-onset, long-duration background insulin and Ultralente injections with variable absorption characteristics and overlapping durations.

All preanalogue insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation. Thus, a detectable effect for regular insulin is delayed by 30-60 min after injection. This, in turn, requires delaying the meal 30-60 min after the injection for optimal effect—a delay rarely attained in a busy child's life. Regular insulin has a wide peak and a long tail for bolus insulin (Figs. 589-6 and 589-7). This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia. These unwanted between-meal effects often necessitate "feeding the insulin" with snacks and limiting the overall degree of blood glucose control. Neutral protamine Hagedorn (NPH) and Lente insulins also have inherent limits because they do not create a peakless background insulin level (see Fig. 589-7C-E). This produces a significant hypoglycemic effect during the midrange of their duration. Thus, it is often difficult to predict their interaction with fast-acting insulins. When regular insulin is combined with NPH or Lente (see Fig. 589-7E), the composite insulin profile poorly mimics normal endogenous insulin secretion. Lente and Ultralente insulins have been discontinued and are no longer available.

Lispro and aspart, insulin analogs, are absorbed much quicker because they do not form hexamers. They provide discrete pulses with little if any overlap and short tail effect. This allows better control of postmeal glucose increase and reduces between-meal or nighttime...
Glargine may be given every 12 hr in young children if a single daily dose of glargine does not produce complete 24 hr basal coverage. The basal insulin glargine should be 25-30% of the total dose in toddlers and 40-50% in older children. The remaining portion of the total daily dose is provided as bolus insulin that is dosed by both the carbohydrate content of the meal as well as the preprandial glucose value.

Hypoglycemia (see Fig. 589-7A). The long-acting analog glargine creates a much flatter 24 hr profile, making it easier to predict the combined effect of a rapid bolus (lispro or aspart) on top of the basal insulin, producing a more physiologic pattern of insulin effect (see Fig. 589-7A). Postprandial glucose elevations are better controlled, and between-meal and nighttime hypoglycemia are reduced.

Glargine may be given every 12 hr in young children if a single daily dose of glargine does not produce complete 24 hr basal coverage. The basal insulin glargine should be 25-30% of the total dose in toddlers and 40-50% in older children. The remaining portion of the total daily dose is provided as bolus insulin that is dosed by both the carbohydrate content of the meal as well as the preprandial glucose value.
Frequent blood glucose monitoring and insulin adjustment are necessary in the 1st weeks as the child returns to routine activities and adapts to a new nutritional schedule, and as the total daily insulin requirements are determined. The major physiologic limit to tight control is hypoglycemia. Use of insulin analogs moderates but does not eliminate this problem.

Some families may be unable to administer 4 daily injections. In these cases, a compromise may be needed. A 3 injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid-acting analog bolus at supper, and glargine at bedtime may provide fair glucose control. Further compromise to a 2 injection regimen may occasionally be needed and frequently involves use of premix insulin (e.g., 70/30).

Insulin Pump Therapy
Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens. Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the insulin to carbohydrate ratio and the correction scale for premeal glucose levels. The patient can enter the patient's blood glucose level and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin bolus dose. Although CSII frequently improves metabolic control, this may not always be the case. The degree of glycemic control is mainly dependent on how closely patients adhere to the principles of diabetes self-care, regardless of the type of intensive insulin regimen. One benefit of pump therapy may be a reduction in severe hypoglycemia and associated seizures. Randomized trials comparing multiple daily insulin regimens using glargine insulin and CSII in children with T1DM demonstrate similar metabolic control and frequency of hypoglycemic events.

Continuous Glucose Monitoring Systems
Subcutaneous glucose sensors that continuously measure interstitial fluid glucose levels are available and approved for use in children. The 1st generation of continuous glucose monitors provided blood glucose data only after downloading by the physician, and did not provide real-time feedback to the patient. This type of device did not appear to improve glycemic control in children, although there was some educational value in detecting patterns of blood glucose fluctuations and episodes of hypoglycemia during periods of sleep.

The newer generation of continuous monitors report blood glucose levels to the patient in real time. Short-term studies indicate clinical benefits of these devices as compared to conventional methods of blood glucose monitoring, when used by motivated and well-informed patients. These devices do not directly control insulin administration but provide glucose readings to permit finer control of insulin administration by patients and families. To avoid hypoglycemia the glucose sensor sounds an alarm; many episodes of hypoglycemia occur at night and unfortunately the parent may sleep through the alarm. Studies are currently evaluating the efficacy of a fully automated closed-loop system of insulin delivery based on continuous glucose sensing, sometimes mistakenly known as an “artificial pancreas” (Fig. 589-8). Some automated glycemic systems employ a bihormonal approach (insulin, glucagon) or have an automated insulin suspension program to ensure normal glycemia while avoiding hypoglycemia. The latter hypoglycemia threshold insulin suspension feature greatly reduces the incidence of hypoglycemia, especially at night. The FDA has approved an insulin pump in combination with a continuous glucose monitoring system that will stop insulin delivery when interstitial glucose levels fall below a predetermined level.

Amylin-Based Adjunct Therapy
Pramlintide acetate, a synthetic analog of amylin, may be of therapeutic value combined with insulin therapy. In adolescents it has been shown to decrease postprandial hyperglycemia, insulin dosage, gastric emptying, and HbA1c levels. It is given as a subcutaneous dose before meals.

Basic and Advanced Diabetes Education
Therapy consists not only of initiation and adjustment of insulin dose but also of education of the patient and family. Teaching is most efficiently provided by experienced diabetes educators and nutritionists.
In the acute phase, the family must learn the “basics,” which includes monitoring the child’s blood glucose and urine and/or blood ketones, preparing and injecting the correct insulin dose subcutaneously at the proper time, recognizing and treating low blood glucose reactions, and having a basic meal plan. Most families are trying to adjust psychologically to the new diagnosis of diabetes in their child and thus have a limited ability to retain new information. Written materials covering these basic topics help the family during the 1st few days.

Children and their families are also required to complete advanced self-management classes in order to facilitate implementation of flexible insulin management. These educational classes will help patients and their families acquire skills for managing diabetes during athletic activities and sick days.

**Ketoacidosis**

Severe insulinopenia (or lack of effective insulin action) results in a physiologic cascade of events in 3 general pathways:
1. Excessive glucose production coupled with reduced glucose utilization raises serum glucose. This produces an osmotic diuresis, with loss of fluid and electrolytes, dehydration, and activation of the renin–angiotensin–aldosterone axis with accelerated potassium loss. If glucose elevation and dehydration are severe and persist for several hours, the risk of cerebral edema increases.
2. Increased catabolic processes result in cellular losses of sodium, potassium, and phosphate.
3. Increased release of free fatty acids from peripheral fat stores supplies substrate for hepatic ketoacid production. When ketoacids accumulate, buffer systems are depleted and a metabolic acidosis ensues. Therapy must address both the initiating event in this cascade (insulinopenia) and the subsequent physiologic disruptions.

Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema. Any protocol must be used with caution and close monitoring of the patient. Adjustments based on sound medical judgment may be necessary for any given level of DKA (Table 589-6).

**Hyperglycemia and Dehydration**

Insulin must be given at the beginning of therapy to accelerate movement of glucose into cells, to subdue hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver. An initial insulin bolus does not speed recovery and may increase the risk of hypokalemia and hypoglycemia. Therefore, insulin infusion is typically begun without a bolus at a rate of 0.1 units/kg/hr. This approximates maximal insulin output in normal subjects during an oral glucose tolerance test. Rehydration also lowers glucose levels by improving renal perfusion and enhancing renal excretion. The combination of these therapies usually causes a rapid initial decline in serum glucose levels. Once glucose goes below 180 mg/dL (10 mmol/L), the osmotic diuresis stops and rehydration accelerates without further increase in the infusion rate.

Repair of hyperglycemia occurs well before correction of acidosis. Therefore, insulin is still needed to control fatty acid release and ketosis after normal glucose levels are reached. To continue the insulin infusion without causing hypoglycemia, glucose must be added to the infusion. We typically recommend that glucose be added as a 5% solution when the serum glucose has decreased <300 mg/dL and as a 10% solution when the serum glucose has decreased <200 mg/dL. The insulin infusion can also be lowered from the initial maximal rate if, despite the above outlined interventions, the serum glucose falls further.

Repair of fluid deficits must be tempered by the potential risk of cerebral edema. It is prudent to approach any child in any hypotonic state with caution and rehydration. The effective serum osmolality \( (\text{Osm}_{\text{serum}} = 2 \times [\text{Na}_{\text{uncorrected}}] + [\text{glucose}]) \) is an accurate index of tonicity of the body fluids, reflecting intracellular and extracellular hydration better than measured plasma osmolality. It is calculated with sodium and glucose in mmol/L. This value is usually elevated at the beginning of therapy and should steadily normalize. A rapid decline, or a slow decline to a subnormal range, may indicate an excess of free water entering the vascular space and an increasing risk of cerebral edema. Therefore, patients should not be allowed oral fluids until rehydration is well underway and significant electrolyte shifts are no longer likely. Limited ice chips may be given as a minimal oral intake. All fluid intake and output should be closely monitored.

Calculation of fluid deficits using clinical signs is difficult in children with DKA because intravascular volume is better maintained in the hypertonic state. For any degree of tachycardia, delayed capillary refill, decreased skin temperature, or orthostatic blood pressure change, the child with DKA will be more dehydrated than the child with a normotonic fluid deficit. The protocol in Table 589-6 corrects a deficit of 85 mL/kg (8.5% dehydration) for all patients in the 1st 24 hr. Children with mild DKA rehydrate earlier and can be switched to oral intake,

### Table 589-6 Diabetic Ketoacidosis Treatment Protocol

<table>
<thead>
<tr>
<th>TIME</th>
<th>THERAPY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hr</td>
<td>10-20 mL/kg IV bolus 0.9% NaCl or LR</td>
<td>Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema</td>
</tr>
<tr>
<td>2nd hr until DKA resolution</td>
<td>0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar &gt;250 mg/dL (14 mmol/L)</td>
<td>IV rate = ( \frac{85 , \text{mL/kg}}{23 , \text{hr}} ) + maintenance – bolus &lt;br&gt; If K &lt;3 mEq/L, give 0.5-1.0 mEq/kg as oral K solution or increase IV K to 80 mEq/L</td>
</tr>
<tr>
<td>Variable</td>
<td>Oral intake with subcutaneous insulin</td>
<td>No emesis; CO2 ≥16 mEq/L, normal electrolytes</td>
</tr>
</tbody>
</table>

Note that the initial IV bolus is considered part of the total fluid allowed in the 1st 24 hr and is subtracted before calculating the IV rate.

Maintenance (24 hr) = 100 mL/kg (for the first 10 kg) + 50 mL/kg (for the second 10 kg) + 25 mL/kg (for all remaining kg)

**Sample calculation for a 30-kg child:** 1st hr = 300 mL IV bolus 0.9% NaCl or LR

\[ \text{2nd and subsequent hr} = \left( \frac{85 \, \text{mL} \times 30}{23 \, \text{hr}} \right) - \left( \frac{1750 \, \text{mL} - 300 \, \text{mL}}{175 \, \text{mL}} \right) = 175 \, \text{mL/hr} \]

\[ \left(0.45\% \text{NaCl with 20 mEq/L Kphos and 20 mEq/L KAc} \right) \]

DKA, diabetic ketoacidosis; I/O, input and output (urine, emesis); K, potassium; KAc, potassium acetate; KPhos, potassium phosphate; LR, lactated Ringer solution; NaCl, sodium chloride; NPO, nothing by mouth.
whereas those with severe DKA and a greater volume deficit require 30-36 hr with this protocol. This more gradual rehydration of the child with severe DKA is an inherent safety feature. The initial intravenous bolus (20 mL/kg of glucose-free isotonic sodium salt solution such as Ringer lactate or 0.9% sodium chloride) for all patients ensures a quick volume expansion and may be repeated if clinical improvement is not quickly seen. This bolus is given as isotonic saline because the patient is inevitably hypertonic, keeping most of the initial infusion in the intravascular space. Subsequent fluid is hypotonic to repair the free water deficit, to allow intracellular rehydration, and to allow a more appropriate replacement of ongoing hypotonic urine losses.

The initial serum sodium is usually normal or low because of the osmolar dilution of hyperglycemia and the effect of an elevated sodium-free lipid fraction. An estimate of the reconstituted, or “true,” serum sodium for any given glucose level above 100 mg/dL (5.6 mmol/L) is calculated as follows:

\[
[\text{Na}^+] + (1.6 \text{ mEq/L} \times \text{Na}^+ \text{ for every 100 mg/dL glucose in excess of 100})
\]

or

\[
[\text{Na}^+] + (1.6 \text{ mEq/L} \times \text{Na}^+ \text{ for every 5.6 mmol/L glucose in excess of 5.6})
\]

The sodium should increase by approximately 1.6 mmol/L for each 100 mg/dL. decline in the glucose. The corrected sodium is usually normal or slightly elevated and indicates moderate hypernatremic dehydration. If the corrected value is greater than 150 mmol/L, severe hypernatremic dehydration may be present and may require slower fluid replacement. The sodium should steadily increase with therapy. Declining sodium may indicate excessive free water accumulation and increased risk of cerebral edema.

**Catabolic Losses**

Both the metabolic shift to a catabolic predominance and the acidosis move potassium and phosphate from the cell to the serum. The osmotic diuresis, the kaliuretic effect of the hyperaldosteronism, and the ketonuria then accelerate renal losses of potassium and phosphate. Sodium is also lost with the diuresis, but free water losses are greater than isotonic losses. With prolonged illness and severe DKA, total body losses can approach 10-13 mEq/kg of sodium, 5-6 mEq/kg of potassium, and 4-5 mEq/kg of phosphate. These losses continue for several hours during therapy until the catabolic state is reversed and the diuresis is controlled. For example, 50% of infused sodium may be lost in the urine during IV therapy. Even though the sodium deficit may be repaired within 24 hr, intracellular potassium and phosphate may not be completely restored for several days.

Although patients with DKA have a total body potassium deficit, the initial serum level is often normal or elevated. This is caused by the movement of potassium from the intracellular space to the serum, both as part of the ketoacid buffering process and as part of the catabolic shift. These effects are reversed with therapy, and potassium returns to the cell. Improved hydration increases renal blood flow, allowing for increased excretion of potassium in the elevated aldosterone state. The net effect is often a dramatic decline in serum potassium levels, especially in severe DKA, and can precipitate changes in cardiac conductivity, flattening of T waves, and prolongation of the QRS complex and can cause skeletal muscle weakness or ileus. The risk of myocardial dysfunction is increased with shock and acidosis. Potassium levels must be closely followed and electrocardiographic monitoring continued until DKA is substantially resolved. If needed, the parenteral potassium can be increased to 80 mEq/L or an oral supplement can be given if there is no emesis. Rarely, the IV insulin must be temporarily stopped.

It is unclear whether phosphate deficits contribute to symptoms of DKA such as generalized muscle weakness. In pediatric patients, a deficit has not been shown to compromise oxygen delivery via a deficiency of 2,3-diphosphoglycerate. Because the patient will receive an excess of chloride, which may aggravate acidosis, it is prudent to use potassium phosphate rather than potassium chloride as a potassium source. Potassium acetate is also used, because it provides an additional buffer.

Pancreatitis is occasionally seen with DKA, especially if prolonged abdominal distress is present; serum amylase may be elevated. If the serum lipase is not elevated, the amylase is likely nonspecific or salivary in origin. Serum creatinine adjusted for age may be falsely elevated owing to interference by ketones in the autoanalyzer methodology. An initial elevated value rarely indicates renal failure and should be rechecked when the child is less ketonemic. Blood urea nitrogen may be elevated with prerenal azotemia and should be rechecked as the child is rehydrated. Mildly elevated creatine or blood urea nitrogen is not a reason to withhold potassium therapy if good urinary output is present.

**Keto Acid Accumulation**

Low insulin infusion rates (0.02-0.05 units/kg/hr) are usually sufficient to stop peripheral release of fatty acids, thereby eliminating the flow of substrate for ketogenesis. Therefore, the initial infusion rate may be decreased if blood glucose levels go below 150 mg/dL (8 mmol/L) despite the addition of glucose to the infusion. Ketogenesis continues until fatty acid substrates already in the liver are depleted, but this production declines much more quickly without new substrate inflow. Bicarbonate buffers, regenerated by the distal renal tubule and by metabolism of ketone bodies, steadily repair the acidosis once ketoacid production is controlled. Bicarbonate therapy is rarely necessary and may even increase the risk of hypokalemia and cerebral edema.

There should be a steady increase in pH and serum bicarbonate as therapy progresses. Kussmaul respirations should abate and abdominal pain resolve. Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or rarely lactic acidosis. Urine ketones may be positive long after ketoacidosis has resolved because the nitropruside side reaction routinely used to measure urine ketones by dipstick measures only acetocetate. During DKA, most excess ketones are β-hydroxybutyrate, which increases the normal ratio to acetocetate from 3:1 to as high as 8:1. With resolution of the acidosis, β-hydroxybutyrate converts to acetocetate, which is excreted into the urine and detected by the dipstick test. Therefore, persistent ketonuria may not accurately reflect the degree of clinical improvement and should not be relied on as an indicator of therapeutic failure.

All patients with DKA should be checked for initiating events that may have triggered the metabolic decomposition.

**Diabetic Ketoacidosis Protocol**

See Table 589-6.

Even though DKA can be of variable severity, a common approach to all cases simplifies the therapeutic regimen and can be safely used for most children. Fluids are best calculated based on weight, not body surface area (m²), because heights are rarely available for the acutely critically ill child. A standard water deficit (85 mL/kg) is assumed. This amount, when added to maintenance, yields approximately 4 L/m² for children of all sizes. Children with milder DKA recover in 10-20 hr (and need less total IV fluid before switching to oral intake), whereas those with more severe DKA require 30-36 hr with this protocol. Any child can be easily transitioned to oral intake and subcutaneous insulin when DKA has resolved (total CO₂ ≥15 mEq/L; pH >7.30; sodium stable between 135 and 145 mEq/L; no emesis). The first dose of short-acting subcutaneous insulin is given with a meal, and the insulin drip is discontinued approximately 30 min later.

A flow sheet is mandatory for accurate monitoring of changes in acidosis, electrolytes, fluid balance, and clinical status, especially if the patient is transferred from the emergency department to an inpatient setting with new caretakers. This flow sheet is best implemented by a central computer system, which allows for rapid update and wide availability of results, as well as rule-driven highlighting of critical values. A paper flow sheet suffices if it stays with the patient, is kept current, and is reviewed frequently by the physician. Any flow sheet should include columns for serial electrolytes, pH, glucose, and fluid balance. Blood testing should occur every 1-2 hr for children with severe DKA and every 3-4 hr for those with mild to moderate DKA.
Cerebral Edema

Cerebral edema complicating DKA remains the major cause of morbidity and mortality in children and adolescents with T1DM. However, its etiology remains unknown. A case-control study of DKA suggested that baseline acidosis and abnormalities of sodium, potassium, and blood urea nitrogen concentrations were important predictors of risk of cerebral edema. Early bolus administration of insulin and high volumes of fluid were also identified as risk factors. The incidence of cerebral edema in children with DKA has not changed over the past 15-20 yr, despite the widespread introduction of gradual rehydration protocols during this interval. Radiographic imaging is frequently unhelpful in making the diagnosis of cerebral edema. Consequently, each patient must be closely monitored. For all but the mildest cases, this includes frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, posturing, and seizures. Mannitol must be readily available for use at the earliest sign of cerebral edema. The physician must also keep informed of the laboratory changes; hypokalemia or hypoglycemia can occur rapidly. Children with moderate to severe DKA have a higher overall risk and should be treated in an intensive care environment.

Nonketotic Hyperosmolar Coma

This syndrome is characterized by severe hyperglycemia (blood glucose >800 mg/dL), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Respirations are usually shallow, but coexistent metabolic (lactic) acidosis may be manifested by Kussmaul breathing. Serum osmolarity is commonly 350 mOsm/kg or greater. This condition is uncommon in children; among adults, mortality rates are high, possibly in part because of delays in recognition and institution of appropriate therapy. In children, there has been a high incidence of preexisting neurologic damage. Profound hyperglycemia may develop over a period of days and, initially, the obligatory osmotic polyuria and dehydration may be partially compensated for by increasing fluid intake. With progression of disease, thirst becomes impaired, possibly because of alteration of the hypothalamic thirst center by hyperosmolality and, in some instances, because of a preexisting defect in the hypothalamic osmoregulating mechanism.

The low production of ketones is attributed mainly to the hyperosmolarity, which in vitro blunts the lipolytic effect of epinephrine and the antilipolytic effect of residual insulin; blunting of lipolysis by the therapeutic use of β-adrenergic blockers may contribute to the syndrome. Depression of consciousness is closely correlated with the degree of hyperosmolarity in this condition as well as in DKA. Hemocentration may also predispose to cerebral arterial and venous thromboses.

Treatment of nonketotic hyperosmolar coma is directed at rapid repletion of the vascular volume deficit and very slow correction of the hyperosmolar state. One-half isotonic saline (0.45% NaCl; some use normal saline) is administered at a rate estimated to replace 50% of the volume deficit in the 1st 12 hr, and the remainder is administered during the ensuing 24 hr. The rate of infusion and the saline concentration are titrated to result in a slow decline of serum osmolality. When the blood glucose concentration approaches 300 mg/dL, the hydrating fluid should be changed to 5% dextrose in 0.2 normal saline. Approximately 20 mEq/L of potassium chloride should be added to each of these fluids to prevent hypokalemia. Serum potassium and plasma glucose concentrations should be monitored at 2 hr intervals for the 1st 12 hr and at 4 hr intervals for the next 24 hr to permit appropriate adjustments of administered potassium and insulin.

Insulin can be given by continuous intravenous infusion beginning with the 2nd hr of fluid therapy. Blood glucose may decrease dramatically with fluid therapy alone. The IV insulin dosage should be 0.05 units/kg/hr rather than 0.1 units/kg/hr as advocated for patients with DKA.

Nutritional Management

Nutrition plays an essential role in the management of patients with T1DM. This is of critical importance during childhood and adolescence, when appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development. There are no special nutritional requirements for the diabetic child other than those for optimal growth and development. In outlining nutritional requirements for the child on the basis of age, sex, weight, and activity, food preferences, including cultural and ethnic ones, must be considered.

Total recommended caloric intake is based on size or surface area and can be obtained from standard tables (Tables 589-7 and 589-8). The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein. Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited. Complex carbohydrates require prolonged digestion and absorption so that plasma glucose levels increase slowly, whereas glucose from refined sugars, including carbonated beverages, is rapidly absorbed and may cause wide swings in the metabolic pattern; carbonated beverages should be sugar free. Priority should be given to total calories and total carbohydrate consumed rather than its source. Carbohydrate counting has become a mainstay in the nutrition education and management of patients with DM. Patients and their families are provided with information regarding the carbohydrate contents of different foods and food label reading. This allows patients to adjust their insulin dosage to their mealtime carbohydrate intake. The use of carbohydrate counting and insulin to carbohydrate ratios and the use of fast-acting insulin analogs and long-acting basal insulin (detemir and glargine) provide many children with less rigid meal planning. Flexibility in the use of insulin in relation to carbohydrate content of food improves the quality of life.

Although in children there is concern about the potential cumulative effect of saccharin, available data do not support an association of moderate amounts with bladder cancer. Other nonnutritive sweeteners such as aspartame are used in a variety of products. Diets with high fiber content are useful in improving control of blood glucose. Moderate amounts of sucrose consumed with fiber-rich foods such as whole-grain bread may have no more glycemic effect than their low-fiber, sugar-free equivalents.

The intake of fat is adjusted so that the polyunsaturated:saturated ratio is increased to approximately 1.2:1.0, in contrast to the estimated American average of 0.3:1.0. Dietary fats derived from animal sources are, therefore, reduced and replaced by polyunsaturated fats from vegetable sources. Substituting margarine for butter, vegetable oil for

<table>
<thead>
<tr>
<th>Table 589-7</th>
<th>Calorie Needs for Children and Young Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong></td>
<td><strong>KCAL REQUIRED/KG BODY WEIGHT</strong></td>
</tr>
<tr>
<td><strong>CHILDREN</strong></td>
<td></td>
</tr>
<tr>
<td>0-12 mo</td>
<td>120</td>
</tr>
<tr>
<td>1-10 yr</td>
<td>100-75</td>
</tr>
<tr>
<td><strong>YOUNG WOMEN</strong></td>
<td></td>
</tr>
<tr>
<td>11-15 yr</td>
<td>35</td>
</tr>
<tr>
<td>≥16 yr</td>
<td>30</td>
</tr>
<tr>
<td><strong>YOUNG MEN</strong></td>
<td></td>
</tr>
<tr>
<td>11-15 yr</td>
<td>80-55 (65)</td>
</tr>
<tr>
<td>16-20 yr</td>
<td></td>
</tr>
<tr>
<td>Average activity</td>
<td>40</td>
</tr>
<tr>
<td>Very physically active</td>
<td>50</td>
</tr>
<tr>
<td>Sedentary</td>
<td>30</td>
</tr>
</tbody>
</table>

Numbers in parentheses are means.
*Gradual decline in calories per unit weight as age increases.

animal oils in cooking, and lean cuts of meat, poultry, and fish for fatty meats is advisable. The intake of cholesterol is also reduced by these measures and by limiting the number of egg yolks consumed. These are advisable. The intake of cholesterol is also reduced by these measures. Therefore, 12-20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful. Navy use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school. Snacks: Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens). Alternative sweeteners: Use of a variety of sweeteners is suggested. Educational techniques: No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required. Eating disorders: Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder. Exercise: Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.


**Table 589-8** Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>(%) OF CALORIES</th>
<th>RECOMMENDED DAILY INTAKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>Will vary</td>
<td>High fiber, especially soluble fiber, optimal amount unknown</td>
</tr>
<tr>
<td>Fiber</td>
<td>&gt;20 g/day</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>12-20</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>Saturated</td>
<td>&lt;10</td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>6-8</td>
<td></td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>Remainder of fat allowance</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>300 mg</td>
<td>Avoid excessive; limit to 3,000-4,000 mg if hypertensive</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ADDITIONAL RECOMMENDATIONS**

_Energy:_ If using measured diet, reevaluate prescribed energy level at least every 3 mo.

_Protein:_ High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12-20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.

_Alcohol:_ Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.

**Snacks:** Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).

_Alternative sweeteners:_ Use of a variety of sweeteners is suggested.

_Educational techniques:_ No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.

_Eating disorders:_ Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.

**Exercise:** Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.

Beer glucose monitoring has been markedly enhanced by the availability of strips impregnated with glucose oxidase that permit blood glucose measurement from a drop of blood. A portable calibrated reflectance meter can approximate the blood glucose concentration accurately. Many meters contain a memory "chip" enabling recall of each measurement, its average over a given interval, and the ability to display the pattern on a computer screen. Such information is a useful educational tool for verifying degree of control and modifying recommended regimens. A small, spring-loaded device that automates capillary bloodletting (lancing device) in a relatively painless fashion is commercially available. Parents and patients should be taught to use these devices and measure blood glucose at least 4 times daily—before breakfast, lunch, and supper, and at bedtime. When insulin therapy is initiated and when adjustments are made that may affect the overnight blood glucose levels, self-monitoring of blood glucose should also be performed at 12 midnight and 3 AM to detect nocturnal hypoglycemia. Ideally, the blood glucose concentration should range from approximately 80 mg/dL in the fasting state to 140 mg/dL after meals. In practice, however, a range is acceptable, based on age of the patient (Table 589-9).

Blood glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose. If the fasting blood glucose is high, the evening dose of long-acting insulin is increased by 10-15% and/or additional fast-acting insulin (lispro or aspart) coverage for bedtime snack may be considered. If the noon glucose level exceeds set limits, the morning fast-acting insulin (lispro or aspart) is increased by 10-15%. If the presupper glucose is high, the noon dose of fast-acting insulin is increased by 10-15%. If the prebedtime glucose is high, the presupper dose of fast-acting insulin is increased by 10-15%. Similarly, reductions in the insulin type and dose should be made if the corresponding blood glucose measurements are consistently below desirable limits.

A minimum of 4 daily blood glucose measurements should be performed. However, some children and adolescents may need to have more frequent blood glucose monitoring based on their level of physical activity and history of frequent hypoglycemic reactions. Families should be encouraged to become sufficiently knowledgeable about managing diabetes. They can maintain near-normal glycemia for prolonged periods by self-monitoring of blood glucose levels before and after meals.
Diabetes

Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A1c for Each Age Group

<table>
<thead>
<tr>
<th>AGE GROUP (yr)</th>
<th>TARGET PREMEAL BG RANGE (mg/dL)</th>
<th>30-DAY AVERAGE BG RANGE (mg/dL)</th>
<th>TARGET HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>100-200</td>
<td>180-250</td>
<td>7.5-9.0</td>
</tr>
<tr>
<td>5-11</td>
<td>80-150</td>
<td>150-200</td>
<td>6.5-8.0</td>
</tr>
<tr>
<td>12-15</td>
<td>80-130</td>
<td>120-180</td>
<td>6.0-7.5</td>
</tr>
<tr>
<td>16-18</td>
<td>70-120</td>
<td>100-150</td>
<td>5.5-7.0</td>
</tr>
</tbody>
</table>

In our laboratory, the nondiabetic reference range for HbA1c is 4.5-5.7% (95% confidence interval).

BG, blood glucose; HbA1c, hemoglobin A1c.

2 hr after meals, and in conjunction with multiple daily injections of insulin, adjusted as necessary.

A continuous glucose monitoring system (CGMS) records data obtained from a subcutaneous sensor every 5 min for up to 72 hr and provides the clinician with a continuous profile of tissue glucose levels. The interstitial glucose levels lag about 13 min behind the blood glucose values at any given level. The CGMS values tend to have a high correlation coefficient for blood glucose values ranging between 40 and 400 mg/dL. CGMS is minimally invasive and entails the placement of a small, subcutaneous catheter that can be easily worn by adults and children. The system provides information that allows the patient and healthcare team to adjust the insulin regimen and the nutrition plan to improve glycemic control. CGMS can be helpful in detecting asymptomatic nocturnal hypoglycemia as well as in lowering HbA1c values without increasing the risk for severe hypoglycemia. Although there are potential pitfalls in CGMS use, including suboptimal compliance, human error, incorrect technique, and sensor failure, the implementation of CGMS in ambulatory diabetes practice allows the clinician to diagnose abnormal glycemic patterns in a more precise manner.

Real-Time Continuous Glucose Monitoring

Real-time continuous glucose monitoring is a technology with the potential of transforming current concepts of glycemic control and optimal diabetes management. In addition to displaying real-time glucose data, newer generations of continuous glucose monitors also have alarms that can be set at below or above predetermined blood glucose thresholds. This safety feature can help parents of young children to recognize nocturnal hypoglycemia. In addition, continuous glucose monitoring shows the rate and direction of glucose change and alerts patients to trends that could lead to dangerous hypoglycemia or hyperglycemia. However, the use of continuous glucose monitoring without clinical decision-making algorithms and guidelines has not been proven to be very effective in improving glycemic control.

Glycosylated Hemoglobin

A reliable index of long-term glycemic control is provided by measurement of glycosylated hemoglobin. HbA1c represents the fraction of hemoglobin to which glucose has been nonenzymatically attached in the bloodstream. The formation of HbA1c is a slow reaction that is dependent on the prevailing concentration of blood glucose; it continues irreversibly throughout the red blood cell’s life span of approximately 120 days. The higher the blood glucose concentration and the longer the red blood cell’s exposure to it, the higher is the fraction of HbA1c, which is expressed as a percentage of total hemoglobin. Because a blood sample at any given time contains a mixture of red blood cells of varying ages, exposed for varying times to varying blood glucose concentrations, an HbA1c measurement reflects the average blood glucose concentration from the preceding 2-3 mo. When measured by standardized methods to remove labile forms, the fraction of HbA1c is not influenced by an isolated episode of hyperglycemia.

It is recommended that HbA1c measurements be obtained 3-4 times/yr to obtain a profile of long-term glycemic control. The lower the HbA1c level, the more likely it is that microvascular complications such as retinopathy and nephropathy will be less severe, delayed in appearance, or even avoided altogether. Depending on the method used for determination, HbA1c values may be spuriously elevated in thalassemia (or other conditions with elevated hemoglobin F) and spuriously lower in sickle cell disease (or other conditions with high red blood cell turnover). Although values of HbA1c may vary according to the method used for measurement, in individuals without diabetes, the HbA1c fraction is usually less than 6%; in individuals with diabetes, values of 6-7.5% represent good metabolic control, values of 7.6-9.9%, fair control, and values of 10% or higher, poor control. The target HbA1c of <7.5% is the same regardless of the patient’s age (see Table 589-9).

Exercise

No form of exercise, including competitive sports, should be forbidden to the child with diabetes. A major complication of exercise in patients with diabetes is the presence of a hypoglycemic reaction during or within hours after exercise. If hypoglycemia does not occur with exercise, adjustments in diet or insulin are not necessary, and glucose regulation is likely to be improved through the increased utilization of glucose by muscles. The major contributing factor to hypoglycemia with exercise is an increased rate of absorption of insulin from its injection site. Higher insulin levels dampen hepatic glucose production so that it is inadequate to meet the increased glucose utilization of exercising muscle. Regular exercise also improves glucose regulation by increasing insulin receptor number. In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counterregulatory hormones.

Benefits of Improved Glycemic Control

The Diabetes Control and Complications Trial (DCCT) established conclusively the association between higher glucose levels and long-term microvascular complications. Intensive management produced dramatic reductions of retinopathy, nephropathy, and neuropathy by 47-76%. The data from the adolescent cohort demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications.

The beneficial effect of intensified treatment was determined by the degree of blood glucose normalization, independently of the type of intensified treatment used. Frequent blood glucose monitoring was considered an important factor in achieving better glycemic control for the intensively treated adolescents and adults. Patients who were intensively treated had individualized glucose targets, frequent adjustments based on ongoing capillary blood glucose monitoring, and a team approach that focused on the person with diabetes as the prime initia
tor of ambulatory care. Care was constantly adjusted toward reaching normal or near-normal glycemic goals while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a preventive approach to blood glucose fluctuations with constant readjustment to counterbalance any high or low blood glucose readings. Target blood glucose goals were adjusted upward if hypoglycemia could not be prevented.

Total duration of diabetes contributes to development and severity of complications. Nonetheless, many professionals have concerns...
about applying the results of the DCCT to preschool-age children, who often have hypoglycemia unawareness with unique safety issues, and to prepubertal school-age children, who were not included in the DCCT. When the DCCT ended in 1993, researchers continued to study more than 90% of participants. The follow-up study, called Epidemiology of Diabetes Interventions and Complications (EDIC), was assessing the incidence and predictors of cardiovascular disease events such as heart attack, stroke, or needed heart surgery, as well as diabetic complications related to the eye, kidney, and nerves. The EDIC demonstrated that intensive blood glucose control reduced risk of any cardiovascular disease event by 42%. In addition, intensive therapy reduced risk of nonfatal heart attack, stroke, or death from cardiovascular causes by 57%.

**Current Intensive Insulin Replacement Regimens**

The goal of physiologic insulin replacement for T1DM is accomplished with short-acting insulins that more closely mimic the sharp increase and short duration of pancreatic insulin secreted with nutrient intake. The rapid-acting insulin analog lispro has superior pharmacokinetic properties for the control of postprandial glucose. Improved postprandial glucose responses occur with twice-daily injections (conventional insulin), multiple daily insulin injections, or CSII. The use of lispro or aspart insulin reduces the frequency of between-meal hypoglycemic events, especially when it is carefully balanced with the carbohydrate content of meal.

The carbohydrate content of food does not influence glycemic control if premeal rapid-acting insulin (bolus) is adjusted to the carbohydrate content of the meal. Wide variations in carbohydrate intake do not modify long-acting (detemir or glargine) or basal insulin requirements. Insulin replacement strategies stress the importance of administering smaller doses of insulin throughout the day. This approach allows insulin doses to be changed as needed to correct hyperglycemia, supplement for additional anticipated carbohydrate intake, or subtract for exercise. Indeed, bolus-based treatment with multiple injections is better adapted to the physiologic profiles of insulin and glucose and can therefore provide better glycemic control than the conventional 2-3 dose regimen. Age-adjusted and individualized insulin to carbohydrate ratios and insulin dosage adjustment algorithms have been developed to normalize elevated blood glucose levels and to compensate for alterations in carbohydrate intake. The use of flexible multiple daily injections and CSII in children with T1DM improves glycemic control without an increase in the incidence of severe hypoglycemia.

**Hypoglycemic Reactions**

Hypoglycemia is the major limitation to tight control of glucose levels. Once injected, insulin absorption and action are independent of the glucose level, thus creating a unique risk of hypoglycemia from an unbalanced insulin effect. Insulin analogs may help reduce but cannot eliminate this risk. Most children with T1DM can expect mild hypoglycemia each week, moderate hypoglycemia a few times each year, and severe hypoglycemia every few years. These episodes are usually not predictable, although exercise, delayed meals or snacks, and wide swings in glucose levels increase the risk. Infants and toddlers are at higher risk for hypoglycemia because they have more variable meals and activity levels, are unable to recognize early signs of hypoglycemia, and are limited in their ability to seek a source of oral glucose to reverse the hypoglycemia. The very young have an increased risk of permanently reduced cognitive function as a long-term sequela of severe hypoglycemia. For this reason, a more relaxed degree of glucose control is necessary until the child matures (see Table 589-9).

Hypoglycemia can occur at any time of day or night. Early symptoms and signs (mild hypoglycemia) may occur with a sudden decrease in blood glucose to levels that do not meet standard criteria for hypoglycemia in children without diabetes. The child may show pallor, sweating, apprehension or fussiness, hunger, tremor, and tachycardia, all as a result of the surge in catecholamines as the body attempts to counter the excessive insulin effect. Behavioral changes such as tearfulness, irritability, and aggression are more prevalent in children. As glucose levels decline further, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia), progressing to inability to seek help and seizures or coma (severe hypoglycemia). Prolonged severe hypoglycemia can result in a depressed sensorium or stroke-like focal motor deficits that persist after the hypoglycemia has resolved. Although permanent sequelae are rare, severe hypoglycemia is frightening for the child and family and can result in significant reluctance to attempt even moderate glycemic control afterward.

Important counterregulatory hormones in children include growth hormone, cortisol, epinephrine, and glucagon. The latter 2 seem more critical in the older child. Many older patients with long-standing T1DM lose their ability to secrete glucagon in response to hypoglycemia. In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy. This substantially increases the risk of hypoglycemia because the early warning signals of a declining glucose level are as a result of catecholamine release. Recurrent hypoglycemic episodes associated with tight metabolic control may aggravate partial counterregulatory deficiencies, producing a syndrome of hypoglycemia unawareness and reduced ability to restore euglycemia (hypoglycemia-associated autonomic failure). Avoidance of hypoglycemia allows some recovery from this unawareness syndrome.

The most important factors in the management of hypoglycemia are an understanding by the patient and family of the symptoms and signs of the reaction and an anticipation of known precipitating factors such as gym or sports activities. Tighter glucose control increases the risk. Families should be taught to look for typical hypoglycemic scenarios or patterns in the home blood glucose log, so that they may adjust the insulin dose and avert predictable episodes. A source of emergency glucose should be available at all times and places, including at school and during visits to friends. If possible, it is important to document the hypoglycemia before treating, because some symptoms may not always be from hypoglycemia. Any child suspected of having a moderate to severe hypoglycemic episode should be treated before testing. It is important not to give too much glucose; 5-10 g should be given as juice or a sugar-containing carbonated beverage or candy, and the blood glucose checked 15-20 min later. Patients, parents, and teachers should also be instructed in the administration of glucagon when the child cannot take glucose orally. An injection kit should be kept at home and school. The intramuscular dose is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg. This produces a brief release of glucose from the liver. Glucagon often causes emesis, which precludes giving oral supplementation if the blood glucose declines after the glucagon effects have waned. Caretakers must then be prepared to take the child to the hospital for IV glucose administration, if necessary. Minidose glucagon (10 µg/kg at age up to a maximum of 150 µg subcutaneously) is effective in treating hypoglycemia in children with blood glucose less than 60 mg/dL who fail to respond to oral glucose and remain symptomatic.

**Dawn Phenomenon and Somogyi Phenomenon**

There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common is a simple decline in insulin levels. This usually results in routinely elevated morning glucose. The dawn phenomenon is thought to be mainly caused by overnight growth hormone secretion and increased insulin clearance. It is a normal physiologic process seen in most adolescents without diabetes, who compensate with more insulin output. A child with T1DM cannot compensate. The dawn phenomenon is usually recurrent and modestly elevates most morning glucose levels.

Rarely, high morning glucose is caused by the Somogyi phenomenon, a theoretical rebound from late-night or early-morning hypoglycemia, though to be from an exaggerated counterregulatory response. It is unlikely to be a common cause, in that most children remain hypoglycemic (do not rebound) once nighttime glucose levels decline. Continuous glucose monitoring systems may help clarify ambiguously elevated morning glucose levels.
Behavioral/Psychologic Aspects and Eating Disorders

Diabetes in a child affects the lifestyle and interpersonal relationships of the entire family. Feelings of anxiety and guilt are common in parents. Similar feelings, coupled with denial and rejection, are equally common in children, particularly during the rebellious teenage years. Family conflict has been associated with poor treatment adherence and poor metabolic control among youths with T1DM. On the other hand, it has been shown that shared responsibility is consistently associated with better psychologic health, good self-care behavior, and good metabolic control, whereas responsibility assumed by either the child or parent alone does not have outcomes that are equally successful. In some cases, links of shared responsibility to health outcomes were stronger among older adolescents. However, no specific personality disorder or psychopathology is characteristic of diabetes; similar feelings are observed in families with other chronic disorders.

COGNITIVE FUNCTION

There is increasing agreement that children with T1DM are at higher risk of developing small differences in cognitive abilities compared to healthy age-matched peers. Evidence suggests that early-onset diabetes (younger than 7 yr) is associated with cognitive difficulties compared to late-onset diabetes and healthy controls. The cognitive difficulties observed were primarily learning and memory skills (both verbal and visual) and attention/executive function skills. It is likely that the impact of diabetes on pediatric cognition appears shortly after diagnosis. Indeed, it has been observed that early-onset diabetes and longer duration of diabetes in children with diabetes adversely affect their school performance and educational achievements.

COPING STYLES

Children and adolescents with T1DM are faced with a complex set of developmental changes as well as shifting burdens of the disease. Adjustment problems might affect psychologic well-being and the course of the disease by impacting self-management and leading to poor metabolic control. Coping styles refer to typical habitual preferences for ways of approaching problems and might be regarded as strategies that people generally use to cope across a wide range of stressors. Problem-focused coping refers to efforts directed toward rational management of a problem, and it is aimed at changing the situation causing distress. On the other hand, emotion-focused coping implies efforts to reduce emotional distress caused by the stressful event and to manage or regulate emotions that might accompany or result from the stressor. In adolescents with diabetes, avoidance coping and venting emotions have been found to predict poor illness-specific self-care behavior and poor metabolic control. Patients who use more mature defenses and exhibit greater adaptive capacity are more likely to adhere to their regimen. Coping strategies seem to be age dependent, with adolescents using more avoidance coping than younger children with diabetes.

NONADHERENCE

Family conflict, denial, and feelings of anxiety or loss of control find expression in nonadherence to instructions regarding nutritional and insulin therapy and in noncompliance with self-monitoring. When adolescents perceive their parents' involvement as criticism, or when they externalize behavior problems, such behaviors interfere with adherence and may result in deterioration of glycemic control. Such behaviors are very common, whereas episodes of deliberate overdosage with insulin resulting in hypoglycemia, or omission of insulin resulting in ketoacidosis, are far less prevalent. They may, however, be pleas for psychologic help or be manipulative attempts to escape an environment perceived as undesirable or intolerable; occasionally, they may be manifestations of suicidal intent. Frequent admissions to the hospital for ketoacidosis or hypoglycemia should arouse suspicion of an underlying emotional conflict. Overprotection on the part of parents is common and often is not in the best interest of the adolescent patient. Feelings of being different or of being alone, or both, are common and must be acknowledged, but may be addressed by tailoring the insulin administration and timing of meals and blood sugar testings in order to allow for a more individualized lifestyle. Families and patients worry about the risk of complications from diabetes, aggregating what they know about type I and type II diabetes, and worry about the decreased life span. Unfortunately, misinformation abounds about the risks of the development of diabetes in siblings or offspring and of pregnancy in young diabetic women. Even appropriate information may cause further anxiety.

All of these issues must be spoken about at the outset, and many of these problems can be averted through continued empathic counseling based on correct information, focusing on normality and on planning to be a productive member of society. Recognizing the potential impact of these problems, peer discussion groups have been organized in many locales; feelings of isolation and frustration tend to be lessened by the sharing of common problems. Summer camps for diabetic children afford an excellent opportunity for learning and sharing under expert supervision. Education about the pathophysiology of diabetes, insulin dose, technique of administration, nutrition, exercise, and hypoglycemic reactions can be reinforced by medical and paramedical personnel. The presence of numerous peers with similar problems offers new insights to the diabetic child. Residential treatment for children and adolescents with difficult to manage T1DM is an option available only in some centers.

ANXIETY AND DEPRESSION

It has been shown that there are significant correlations between poor metabolic control and depressive symptoms, a high level of anxiety, or a previous psychiatric diagnosis. In a similar way, poor metabolic control is related to higher levels of personal, social, school maladjustment, or family environment dissatisfaction. It is estimated that 20-26% of adolescent patients may develop major depressive disorder. The prevalence of depression is 2-fold greater than controls in children with diabetes and 3-fold greater in adolescents. The course characteristics of depression in young diabetic subjects and psychiatric control subjects appear to be similar; however, eventual propensity of diabetic youths for more protracted depressions is greater and there is a higher risk of recurrence among young diabetic females. On balance, anxiety and depression play an important and complex role in T1DM; their relationship to metabolic control does not yet appear clear. Therefore, the healthcare providers managing a child or adolescent with diabetes should be aware of their pivotal role as counselor and advisor and should closely monitor the mental health of patients with diabetes.

FEAR OF SELF-INJECTING AND SELF-TESTING

Extreme fear of self-injecting insulin (injection phobia) is likely to compromise glycemic control as well as emotional well-being. Likewise, fear of finger pricks can be a source of distress and may seriously hamper self-management. Children and adolescents may either omit insulin dosing or refuse to rotate their injection sites because repeated injection in the same site is associated with less pain sensation. Failure to rotate injection sites results in subcutaneous scar formation (lipohypertrophy). Insulin injection into the lipohypertrophic skin is usually associated with poor insulin absorption and/or insulin leakage with resultant suboptimal glycemic control. Children and adolescents with injection phobia and fear of self-testing can be counseled by a trained behavioral therapist and benefit from such techniques as desensitization and biofeedback to attenuate pain sensation and psychologic distress associated with these procedures. Another possibility is to consider using an indwelling subcutaneous soft cannula to minimize the discomfort of repeated injections.

EATING DISORDERS

Treatment of T1DM involves constant monitoring of food intake. In addition, improved glycemic control is sometimes associated with increased weight gain. In adolescent females, these 2 factors, along with individual, familial, and socioeconomic factors, can lead to an increased incidence of both nonspecific and specific eating disorders, which can disrupt glycemic control and increase the risk of long-term complications. Eating disorders and subthreshold eating disorders are almost
twice as common in adolescent females with T1DM as in their nondiabetic peers. The reports of the frequencies of specific (anorexia or bulimia nervosa) eating disorders vary from 1.0-6.9% among female patients with T1DM. The prevalence of nonspecific and subthreshold eating disorders is 9% and 14%, respectively. Approximately 11% of T1DM adolescent females take less insulin than prescribed in order to lose weight. Among adolescent females with an eating disorder, approximately 42% of patients misuse insulin, whereas the estimates of insulin misuse prevalence in subthreshold and nondisordered eating groups are 18% and 6%, respectively. Although there is little information regarding the prevalence of eating disorders among male adolescents with T1DM, available data suggest normal eating attitudes in most. Among healthy adolescent males who participate in wrestling, however, the drive to lose weight has led to the seasonal, transient development of abnormal eating attitudes and behaviors, which may lead to insulin dose omission in order to lose weight.

When behavioral/psychologic problems and/or eating disorders are assumed to be responsible for poor adherence with the medical regimen, referral for psychologic evaluation and management is indicated. Behavioral therapists and psychologists usually form part of the pediatric diabetes team in most centers and can help assess and manage emotional and behavioral disorders in diabetic children. Evaluation of nurse-delivered motivational enhancement with and without cognitive behavior therapy in adults revealed the combined therapy resulted in modest improvement in glycemic control. However, motivational enhancement therapy alone did not improve glycemic control. While in some studies the effect of therapist-delivered motivational enhancement therapy on glycemic control in adolescents with T1DM lasted as long as intensive individualized counseling continued, in other studies, motivational interviewing was shown to be an effective method of facilitating changes in a teenager’s behavior with T1DM with corresponding improvement in glycemic control.

Management During Infections

Although infections are no more common in diabetic children than in nondiabetic ones, they can often disrupt glucose control and may precipitate DKA. In addition, the diabetic child is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counterregulatory hormones associated with stress blunt insulin action and elevate glucose levels. If anorexia occurs from ketosis, lack of caloric intake increases the risk of hypoglycemia. Although children younger than 3 yr of age tend to become hypoglycemic and older children tend toward hyperglycemia, the overall effect is unpredictable. Therefore, frequent blood glucose monitoring and adjustment of insulin doses are essential elements of sick day guidelines (Table 589-10).

The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis. This can usually be done at home if proper sick day guidelines are followed and with telephone contact with healthcare providers. The family should seek advice if home treatment does not control ketonuria, hyperglycemia, or hypoglycemia, or if the child shows signs of dehydration. A child with large ketonuria and emesis should be seen in the emergency department for a general examination, to evaluate hydration, and to determine whether ketoacidosis is present by checking serum electrolytes, glucose, pH, and total CO2. A child whose blood glucose declines to less than 50-60 mg/dL (2.8-3.3 mmol/L) and who cannot maintain oral intake may need IV glucose, especially if further insulin is needed to control ketonemia.

Management During Surgery

Surgery can disrupt glucose control in the same way as can intercurrent infections. Stress hormones associated with the underlying condition as well as with surgery itself cause insulin resistance. This increases glucose levels, exacerbates fluid losses, and may initiate DKA. On the other hand, caloric intake is usually restricted, which decreases glucose levels. The net effect is as difficult to predict as during an infection. Vigilant monitoring and frequent insulin adjustments are required to maintain euglycemia and avoid ketosis.

Maintaining glucose control and avoiding DKA are best accomplished with IV insulin and fluids. A simple insulin adjustment scale based on the patient’s weight and blood glucose level can be used in most situations (Table 589-11). The IV insulin is continued after surgery as the child begins to take oral fluids; the IV fluids can be steadily decreased as oral intake increases. When full oral intake is achieved, the IV may be capped and subcutaneous insulin begun. When surgery is elective, it is best performed early in the day, allowing the patient maximal recovery time to restart oral intake and subcutaneous insulin therapy. When elective surgery is brief (less than 1 hr) and full oral intake is expected shortly afterward, one may simply monitor the blood glucose hourly and give a dose of insulin analog according to the child’s home glucose correction scale. If glargine or detemir is used as the basal insulin, a full dose is given the evening before planned surgery. If NPH or Lente is used, one half of the morning dose is given before surgery. The child should not be discharged until blood glucose levels are stable and oral intake is tolerated.

<table>
<thead>
<tr>
<th>Table 589-10</th>
<th>Guidelines for Sick Day Management</th>
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<tr>
<td><strong>URINE KETONE STATUS</strong></td>
<td><strong>GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN</strong></td>
</tr>
<tr>
<td>Negative or small¹</td>
<td>q2hr</td>
</tr>
<tr>
<td>Moderate to large²</td>
<td>q1hr</td>
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Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and Lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.

Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.

Call physician or nurse if blood glucose remains elevated after 3 extra doses, if blood glucose remains less than 70 mg/dL and child cannot take oral supplement; if dehydration occurs.

*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.

¹For home serum ketones <1.5 mmol/L per commercial kit.

²For home serum ketones >1.5 mmol/L.
LONG-TERM COMPLICATIONS: RELATION TO GLYCEMIC CONTROL

Complications of DM can be divided into 3 major categories: (1) microvascular complications, specifically, retinopathy and nephropathy; (2) macrovascular complications, particularly accelerated coronary artery disease, cerebrovascular disease, and peripheral vascular disease; and (3) neuropathies, both peripheral and autonomic, affecting a variety of organs and systems (Table 589-12). In addition, cataracts may occur more frequently.

Diabetic retinopathy is the leading cause of blindness in the United States in adults age 20-65 yr. The risk of diabetic retinopathy after 15 yr duration of diabetes is 98% for individuals with T1DM and 78% for those with T2DM. Rates for diabetic retinopathy range from close to 15% to up to 30%. Lens opacities (caused by glycation of tissue proteins and activation of the polyol pathway) are present in at least 5% of those younger than age 19 yr. The metabolic control has an impact on the development of this complication, as prevalence rates are substantially higher with increased duration of diabetes, and higher HbA1c, blood pressure, and cholesterol. Independent of duration, the prevalence of diabetic retinopathy is higher in T1DM. However, genetic factors also have a role, because only 50% of patients develop proliferative retinopathy. The earliest clinically apparent manifestations of diabetic retinopathy are classified as nonproliferative or background diabetic retinopathy—microaneurysms, dot and blot hemorrhages, hard and soft exudates, venous dilation and beading, and intraretinal microvascular abnormalities. These changes do not impair vision. The more severe form is proliferative diabetic retinopathy, which manifests by neovascularization, fibrous proliferation, and preretinal and vitreous hemorrhages. Proliferative retinopathy, if not treated, is relentlessly progressive and impairs vision, leading to blindness. The mainstay of treatment is panretinal laser photocoagulation.

In advanced diabetic eye disease—manifested by severe vitreous hemorrhage or fibrosis, often with retinal detachment—vitrectomy is an important therapeutic modality. Eventually, the eye disease becomes quiescent, a stage termed involutional retinopathy. A separate subtype of retinopathy is diabetic maculopathy, which is manifested by severe macular edema impairing central vision, for which focal laser photocoagulation may be effective.

Guidelines suggest that diabetic patients have an initial dilated and comprehensive examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with T2DM, and within 3-5 yr after the onset of T1DM (but not before age 10 yr). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both T1DM and T2DM patients should be repeated annually by an ophthalmologist who is experienced in diagnosing the presence of diabetic retinopathy and is knowledgeable about its management (see Table 589-12).

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States. Most ESRD from diabetic nephropathy is preventable. Diabetic nephropathy affects 20-30% of patients with T1DM and 15-20% of T2DM patients 20 yr after onset. The mean 5 yr life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term T1DM may be due to nephropathy, which may account for approximately 50% of deaths. The risk of nephropathy increases with duration of diabetes (up until 25-30 yr duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Only 30-40% of patients affected by T1DM eventually experience ESRD. The glycation of tissue proteins results in glomerular basement membrane thickening. The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate of 30-300 mg/24 hr (20-200 µg/min)—microalbuminuria—can be detected and constitutes an early stage of nephropathy from intermittent to persistent (incipient), which is commonly associated with glomerular hyperfiltration and blood pressure elevation. As nephropathy evolves to early overt stage with proteinuria (albumin excretion rate >300 mg/24 hr, or >200 µg/min), it is accompanied by hypertension. Advanced-stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and...

| Table 589-12 Screening Guidelines |
|----------------------------------|------------------|------------------|------------------|------------------|
| WHEN TO COMMENCE SCREENING       | FREQUENCY        | PREFERRED METHOD OF SCREENING | OTHER SCREENING METHODS | POTENTIAL INTERVENTION |
| Retinopathy                      | After 5 yr duration in prepubertal children, after 2 yr in pubertal children | 1-2 yearly | Fundal photography | Fluorescein angiography, mydriatic ophthalmoscopy | Improved glycemic control, laser therapy |
| Nephropathy                      | After 5 yr duration in prepubertal children, after 2 yr in pubertal children | Annually | Spot urine sample for albumin: creatinine ratio | 24 hr excretion of albumin, urinary albumin: creatinine ratio | Improved glycemic control, blood pressure control, ACE inhibitors |
| Neuropathy                       | Unclear in children; adults at diagnosis in T2DM and 5 yr after diagnosis in T1DM | Unclear | Physical examination | Nerve conduction, thermal and vibration threshold, pupillometry, cardiovascular reflexes | Improved glycemic control |
| Macrovascular disease            | After age 2 yr | Every 5 yr | Lipids | Blood pressure | Statins for hyperlipidemia, blood pressure control |
| Thyroid disease                  | At diagnosis | Every 2-3 yr or more frequently based on symptoms or the presence of antithyroid antibodies | TSH | Thyroid peroxidase, thyroglobulin antibodies | Thyroxine |
| Celiac disease                   | At diagnosis | Every 2-3 yr | Tissue transglutaminase, endomysial antibody | Transglutaminase antibodies | Gluten-free diet |

ACE, angiotensin-converting enzyme; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone.

hypoinsulinemia. Progression to ESRD is recognized by the appearance of uremia, the nephritic syndrome, and the need for renal replacement (transplantation or dialysis).

Screening for diabetic nephropathy is a routine aspect of diabetes care (see Table 589-12). The American Diabetes Association recommends yearly screening for individuals with T2DM and yearly screening for those with T1DM after 5 yr duration of disease (but not before puberty). A random spot urine sample for albumin to creatinine ratio is obtained. Abnormal results should be confirmed by 2 additional specimens on separate days because of the high variability of albumin excretion in patients with diabetes. Short-term hyperglycemia, strenuous exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevation urinary albumin excretion. There is marked day-to-day variability in albumin excretion, so at least 2 of 3 collections done in a 3-6 mo period should show elevated levels before microalbuminuria is diagnosed and treatment is started. Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys: (1) meticulous control of hyperglycemia, (2) aggressive control of systemic blood pressure, (3) selective control of arteriolar dilation by use of angiotensin-converting enzyme inhibitors (thus decreasing transglomerular capillary pressure), and (4) dietary protein restriction (because high protein intake increases the renal perfusion rate). Tight glycemic control will delay the progression of microalbuminuria and slow the progression of diabetic nephropathy. Previous extensive therapy of diabetes has a persistent benefit for 7-8 yr and may delay or prevent the development of diabetic nephropathy.

**DIABETIC NEUROPATHY**

Both the peripheral and autonomic nervous systems can be involved, and adolescents with diabetes can show early evidence of neuropathy. This complication can be traced to the metabolic effects of hyperglycemia and/or other effects of insulin deficiency on the various constituents of the peripheral nerve. The polyol pathway, nonenzymatic glycation, and/or disturbances of myoinositol metabolism affecting 1 or more cell types in the multicellular constituents of the peripheral nerve appear likely to have an inciting role. The role of other factors, such as possible direct neurotrophic effects of insulin, insulin-related growth factors, nitric oxide, and stress proteins, seems to be relevant. Peripheral neuropathy may first present in some adolescents with a long-standing history of diabetes. Using quantitative sensory testing, abnormal cutaneous thermal perception is a common finding in both upper and lower limbs in neurologically asymptomatic young diabetic patients. Heat-induced pain threshold in the hand is correlated with the duration of the diabetes. There is no correlation between quantitative sensory testing scores and metabolic control. Subclinical motor nerve impairment as manifested by reduced sensory nerve conduction velocity and sensory nerve action potential amplitude can be detected during late puberty and after puberty in approximately 10% of adolescents. Poor metabolic control during puberty appears to induce deteriorating peripheral neural function in young patients. An early sign of autonomic neuropathy such as decreased heart rate variability may present in adolescents with a history of long-standing disease and poor metabolic control. A number of therapeutic strategies have been attempted with variable results. These treatment modalities include (1) improvement in metabolic control, (2) use of aldose reductase inhibitors to reduce by-products of the polyol pathway, (3) use of α-lipoic acid (an antioxidant) that enhances tissue nicotinamide and its metabolites, (4) use of anticonvulsants (e.g., lorazepam, valproate, gabapentin, carbamazepine, pregabalin, phenytoin, tiagabine, and topiramate) for treatment of neuropathic pain, and (5) antidepressants (amitriptyline, imipramine, and selective serotonin reuptake inhibitors). Additional medications include antiarrhythmics such as lidocaine, topical analgesics, and nonsteroidal antiinflammatory drugs.

Other quite rarely noted complications in diabetic children include dwarfism associated with a glycogen-laden enlarged liver (Mauriac syndrome), osteopenia, and a syndrome of limited joint mobility associated with tight, waxy skin; growth impairment; and maturational delay. The Mauriac syndrome is related to chronic underinsulinization; it is much less common since longer-acting insulins have become available. Clinical features of Mauriac syndrome include moon face, protuberant abdomen, proximal muscle wasting, and enlarged liver from fat and glycogen infiltration. The syndrome of limited joint mobility is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and nephropathy, which may appear before 18 yr of age. In the past decade or two, the prevalence of limited joint mobility has significantly decreased, which is attributed to the improved overall metabolic control of children and adolescents with T1DM.

**PROGNOSIS**

T1DM is a serious, chronic disease. It has been estimated that the average life span of individuals with diabetes is approximately 10 yr shorter than that of the nondiabetic population. Although diabetic children eventually attain a height within the normal adult range, puberty may be delayed, and the final height may be less than the genetic potential. From studies in identical twins, it is apparent that despite seemingly satisfactory control, the diabetic twin manifests delayed puberty and a substantial reduction in height when onset of disease occurs before puberty. These observations indicate that, in the past, conventional criteria for judging control were inadequate and that adequate control of T1DM was almost never achieved by routine means.

The introduction of portable devices (insulin pumps) that can be programmed to provide CSII with meal-related boluses is 1 approach to the resolution of these long-term problems. In selected individuals, nearly normal patterns of blood glucose and other indices of metabolic control, including HbA₁c, have been maintained for several years. This approach, however, should be reserved for highly motivated persons committed to rigorous self-monitoring of blood glucose who are alert to the potential complications, such as mechanical failure of the infusion device causing hyperglycemia or hypoglycemia and to infection at the site of catheter insertion.

The changing pattern of metabolic control is having a profound influence on reducing the incidence and the severity of certain complications. For example, after 20 yr of diabetes, there is a decline in the incidence of nephropathy in T1DM in Sweden among children whose disease was diagnosed in 1971-1975 compared with in the preceding decade. In addition, in most patients with microalbuminuria in whom it was possible to obtain good glycemic control, microalbuminuria disappeared. This improved prognosis is directly related to metabolic control.

**PANCREAS AND ISLET TRANSPLANTATION AND REGENERATION**

In an attempt to cure T1DM, transplantation of a segment of the pancreas or of isolated islets has been performed in adults. These procedures are both technically demanding and associated with the risks of disease recurrence and complications of rejection or its treatment by immunosuppression. Long-term complications of immunosuppression include the development of malignancy. Some antirejection drugs, notably cyclosporine and tacrolimus, are toxic to the islets of Langerhans, impairing insulin secretion and even causing diabetes. Hence, segmental pancreas transplantation is generally only performed in association with transplantation of a kidney for a patient with ESRD due to diabetic nephropathy in which the immunosuppressive regimen is indicated for the renal transplantation. Several thousand such transplants have been performed in adults. With experience and newer immunosuppressive agents, functional survival of the pancreatic graft may be achieved for up to several years, during which time patients may be in metabolic control with no or minimal exogenous insulin and reversal of some of the microvascular complications. However, because children and adolescents with DM are not likely to have ESRD from the diabetic nephropathy, pancreas transplantation as a primary treatment in children cannot be recommended.

Islet cell transplantation is challenging because of limited survival of the transplanted cells and because of rejection. Research continues to improve techniques for the yield, viability, and reduction of
immunogenicity of the islets of Langerhans for transplantation. An islet transplantation strategy (Edmonton protocol) infused isolated pancreatic islets into the portal vein of a group of adults with T1DM, along with immunosuppressive medications that had lower side-effect profiles than other drugs. While lasting insulin independence was initially low, engraftment and insulin independence have improved over the last decade, and over a thousand patients having undergone the procedure. There has been improved islet engraftment by the use of improved induction and maintenance immunosuppression. Still, in 5-y follow-up studies, only 1 in 20 maintain insulin independence, with an average duration of insulin independence in all of only about 15 mo. Long-term challenges remain the toxicity of immunosuppression, the limited procurement of viable tissue, and funding and limitations of engraftment itself.

Alternative means of generating β cells are being sought from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Regeneration of islets is an approach that could potentially cure T1DM because β-cell mass is actually dynamically regulated.

589.3 Type 2 Diabetes Mellitus
Britta M. Sörensen and Nicholas Josse

Formerly known as non–insulin dependent diabetes or adult-onset diabetes, T2DM is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of the β cell to keep up with increasing insulin demand. Patients with T2DM have relative rather than absolute insulin deficiency. Generally, they are not ketosis prone, but ketoacidosis may develop in some circumstances. The specific etiology is not known, but these patients do not have autoimmune destruction of β cells, nor do they have any of the known causes of secondary diabetes.

NATURAL HISTORY

T2DM is considered a polygenic disease aggravated by environmental factors, such as low physical activity and excessive caloric intake. Most patients are obese, although the disease can occasionally be seen in normal weight individuals. Asians in particular appear to be at risk for T2DM at lower degrees of total adiposity. Some patients may not necessarily meet overweight or obese criteria for age and gender despite abnormally high percentage of body fat in the abdominal region. Obesity, in particular, central obesity, is associated with the development of insulin resistance. In addition, patients who are at risk for developing T2DM exhibit decreased glucose-induced insulin secretion. Obesity does not lead to the same degree of insulin resistance in all individuals and even those who develop insulin resistance do not necessarily exhibit impaired β-cell function. Thus, many obese individuals have some degree of insulin resistance but compensate for it by increasing insulin secretion. Those individuals who are unable to adequately compensate for insulin resistance by increasing insulin secretion, develop IGT and impaired fasting glucose (usually, although not always, in that order). Hepatic insulin resistance leads to excessive hepatic glucose output (failure of insulin to suppress hepatic glucose output), while skeletal muscle insulin resistance leads to decreased glucose uptake in a major site of glucose disposal. Over time hyperglycemia worsens, a phenomenon that has been attributed to the deleterious effect of chronic hyperglycemia (glucotoxicity) or chronic hyperlipidemia (lipotoxicity) on β-cell function and is often accompanied by increased triglyceride content and decreased insulin gene expression. At some point, blood glucose elevation meets the criteria for diagnosis of T2DM (see Table 589-2), but most patients with T2DM remain asymptomatic for months to years after this point because hyperglycemia is moderate and symptoms are not as dramatic as the polyuria and weight loss accompanying T1DM. Weight gain may even continue. The prolonged hyperglycemia may be accompanied by the development of microvascular and macrovascular complications. In time, β-cell function can decrease to the point that the patient has absolute insulin deficiency and becomes dependent on exogenous insulin. In T2DM, insulin deficiency is rarely absolute, so patients usually do not need insulin to survive. Nevertheless, glycemic control can be improved by exogenous insulin. Although DKA is uncommon in patients with T2DM, it can occur and is usually associated with the stress of another illness such as severe infection. DKA tends to be more common in African-American patients than in other ethnic groups. Although it is generally believed that autoimmune destruction of pancreatic β cells does not occur in T2DM, autoimmune markers of T1DM—namely, glutamic acid decarboxylase antibody, ICA512, and insulin-associated autoantibody—may be positive in up to one third of the cases of adolescent T2DM. The presence of these autoimmune markers does not rule out T2DM in children and adolescents. At the same time, because of the general increase in obesity, the presence of obesity does not preclude the diagnosis of T1DM. Although the majority of newly diagnosed children and adolescents can be confidently assigned a diagnosis of T1DM or T2DM, a few exhibit features of both types and are difficult to classify.

EPIDEMIOLOGY

National Health and Nutritional Examination Surveys data (from 1999-2002) show that the prevalence of T2DM in 12-19 yr olds in the United States is 1.46 in 1,000. The Southeastern Aerosol Research and Characterization (SEARCH) study found that the prevalence of type 2 diabetes in the 10-19 yr old age group in the United States was 15% in 2001 and it is likely that this proportion has increased over time. Certain ethnic groups appear to be at higher risk; for example, Native Americans, Hispanic Americans, and African-Americans (in that order) have higher incidence rates than white Americans. Although a majority of children presenting with diabetes still have T1DM, the percentage of children presenting with T2DM is increasing and represents up to 50% of the newly diagnosed children in some centers.

Prevalence in the rest of the world varies widely and accurate data are not available for many countries, but it is clear that the prevalence is increasing in every part of the world. Asians in general seem to develop T2DM at lower body mass index levels than Europeans. In conjunction with their low incidence of type 1 diabetes, this means that T2DM accounts for a higher proportion of childhood diabetes in many Asian countries.

The epidemic of T2DM in children and adolescents parallels the emergence of the obesity epidemic. Although obesity itself is associated with insulin resistance, diabetes does not develop until there is some degree of failure of insulin secretion. Thus, when measured, insulin secretion in response to glucose or other stimuli is always lower in persons with T2DM than in control subjects matched for age, sex, weight, and equivalent glucose concentration.

GENETICS

T2DM has a strong genetic component; concordance rates among identical twins are in the 60-90% range. It should be kept in mind, however, that twinning itself increases the risk of T2DM (because of intrauterine growth restriction) and this may distort estimates of genetic risk. In at least 1 study from Denmark, both monozygotic and dizygotic twins have a lifetime concordance of T2DM of around 70%, indicating that shared environmental factors (including the prenatal environment) may play a large role in the development of T2DM. The genetic basis for T2DM is complex and incompletely defined; no single identified defect predominates as does the HLA association with T1DM. Genomewide association studies have now identified certain genetic polymorphisms that are associated with increased T2DM risk in most populations studied; the most consistently identified are variants of the TCF7L2 (transcription factor 7–like 2) gene, which may have a role in β-cell function. Other identified risk alleles include variants in PPARG and KCNJ11 as well as many others. But to date, all these identified variants explain only a small portion (probably less than 20%) of the population risk of diabetes and in many cases the mechanism by which these polymorphisms confer risk of T2DM is not clear.

EPIGENETICS AND FETAL PROGRAMMING

Low birthweight and intrauterine growth restriction are associated with increased risk of T2DM. This risk appears to be higher in
low-birthweight infants who gain weight more rapidly in the 1st few years of life. These findings have led to the formulation of the “thrifty phenotype” hypothesis, which postulates that poor fetal nutrition somehow programs these children to maximize storage of nutrients and makes them more prone to future weight gain and development of diabetes. Epigenetic modifications may play a role in this phenomenon, but the detailed molecular mechanisms involved have yet to be determined. Whatever the exact mechanism, prenatal and early childhood environments play an important role in the pathogenesis of T2DM and may do so by epigenetic modification of the DNA (in addition to other factors).

ENVIRONMENTAL AND LIFESTYLE-RELATED RISK FACTORS

Obesity is the most important lifestyle factor associated with development of T2DM. This, in turn, is associated with the intake of high-energy foods, physical inactivity, TV viewing (“screen time”), and low socioeconomic status (in developed countries). Maternal smoking also increases the risk of diabetes and obesity in the offspring. Interestingly, smoking by young adults also increases their own risk of diabetes by as yet unknown mechanisms. In addition, sleep deprivation and psychosocial stress are associated with increased risk of obesity in childhood and with IGT in adults, possibly via overactivation of the hypothalamic-pituitary-adrenal axis. Many antipsychotics (especially the atypical antipsychotics like olanzapine and quetiapine) and antidepressants (both tricyclic antidepressants and newer antidepressants like fluoxetine and paroxetine) induce weight gain. In addition to the risk conferred by increased obesity, some of these medications may also have a direct role in causing insulin resistance, β-cell dysfunction, leptin resistance, and activation of inflammatory pathways. To complicate matters further, there is evidence that schizophrenia and depression themselves increase the risk of T2DM and the metabolic syndrome, independent of the risk conferred by drug treatment. As a result, both obesity and T2DM are more prevalent in this population, and with increasing use of antipsychotics and antidepressants in the pediatric population, this association is likely to become stronger.

CLINICAL FEATURES

In the United States, T2DM in children is more likely to be diagnosed in Native American, Hispanic American, and African-American youth, with the highest incidence being reported in Pima Indian youth. While cases may be seen as young as 6 yr of age, most are diagnosed in adolescence and incidence increases with increasing age. Family history of T2DM is present in practically all cases. Typically, patients are obese and present with mild symptoms of polyuria and polydipsia, or are asymptomatic and detected on screening tests. Presentation with DKA occurs in up to 10% of cases. Physical examination frequently reveals the presence of acanthosis nigricans, most commonly on the neck and in other flexural areas. Other findings may include striae and an increased waist:hip ratio. Laboratory testing reveals elevated HbA1c levels. Hyperlipidemia characterized by elevated triglycerides and low-density lipoprotein cholesterol levels is commonly seen in patients with T2DM at diagnosis. Consequently, lipid screening is indicated in all new cases of T2DM. Because hyperglycemia develops slowly and patients may be asymptomatic for months or years after they develop T2DM, screening for T2DM is recommended in high-risk children (Table 589-13). The American Diabetes Association recommends that all youth who are overweight and have at least 2 other risk factors be tested for T2DM beginning at age 10 yr or at the onset of puberty and every 2 yr after that. Risk factors include family history of T2DM in 1st- or 2nd-degree relatives, history of gestational diabetes in the mother, belonging to certain ethnic groups (i.e., Native American, African-American, Hispanic, or Asian/Pacific Islander groups) and having signs of insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome). The current recommendation is to use fasting blood glucose as a screening test, but some authorities now recommend that HbA1c be used as a screening tool. In borderline or asymptomatic cases, the diagnosis may be confirmed using a standard oral glucose tolerance test, but this test is not required if typical symptoms are present or fasting plasma glucose or HbA1c is clearly elevated on 2 separate occasions.

TREATMENT

Type 2 diabetes is a progressive syndrome that gradually leads to complete insulin deficiency during the patient’s life. A systematic approach for treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when hypoglycemic oral agent failure occurs. Nevertheless, lifestyle modification (diet and exercise) is an essential part of the treatment regimen, and consultation with a dietitian is usually necessary. There is no particular dietary or exercise regimen that has been conclusively shown to be superior but most centers recommend a low-calorie, low-fat diet and 30-60 min of physical activity at least 5 times/wk. Screen time should be limited to 1-2 hr/day. Children with T2DM often come from household environments with a poor understanding of healthy eating habits. Commonly observed behaviors include skipping meals, heavy snacking, and excessive daily television viewing, video game playing, and computer use. Adolescents engage in nonappetite-based eating (i.e., emotional eating, television-cued eating, boredom) and cyclic eating (“yo-yo” dieting). Treatment in these cases is frequently challenging and may not be successful unless the entire family buys into the need to change their unhealthy lifestyle.

It is recommended that oral hypoglycemic agents be introduced at the time of diagnosis (Table 589-14). Patients who present with DKA or with markedly elevated HbA1c (>9.0%) will require treatment with insulin using protocols similar to those used for treating T1DM. Once blood glucose levels are under control, most cases can be managed with oral hypoglycemic agents and lifestyle interventions, but some patients will continue to require insulin therapy.

The most commonly used and the only FDA-approved oral agent for the treatment of T2DM in children and adolescents is metformin. Renal function must be assessed before starting metformin as impaired renal function has been associated with potentially fatal lactic acidosis. Significant hepatic dysfunction is also a contraindication to metformin use, although mild elevations in liver enzymes may not be an absolute contraindication. The usual starting dose is 500 mg once daily. This may be increased to a maximum dose of 2,000 mg/day. Abnormal symptoms are common early in the course of treatment, but in most cases they will resolve with time.

Other agents such as thiazolidinediones, sulfonylureas, acarbose, pramlintide, and incretin mimetics are being used routinely in adults but are not used as commonly in pediatrics. Sulfonylureas are widely used in adults, but experience in pediatrics is limited. Sulfonylureas cause insulin release by closing the potassium channel ($K_{ATP}$) on $\beta$-cell membranes.
Table 589-14 | Oral Hypoglycemic Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>DURATION OF BIOLOGIC EFFECT (hr)</th>
<th>USUAL DAILY DOSE (mg)</th>
<th>DOSES/DAY</th>
<th>SIDE EFFECTS</th>
<th>CAUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Insulin sensitizer</td>
<td></td>
<td></td>
<td></td>
<td>Gastrointestinal disturbance, lactic acidosis</td>
<td>Avoid in hepatic or renal impairment</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td>1500-2500</td>
<td>2-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonureas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetohexamide</td>
<td></td>
<td>12-18</td>
<td>500-750</td>
<td>1 or divided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td></td>
<td>27-72</td>
<td>250-500</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td></td>
<td>14-16</td>
<td>1000-2000</td>
<td>1 or divided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td></td>
<td>14-16</td>
<td>2.5-10</td>
<td>1 or divided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td></td>
<td>20-24+</td>
<td>2.5-10</td>
<td>1 or divided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td></td>
<td>24+</td>
<td>2-4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glitaziones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Promote insulin secretion</td>
<td>≤24</td>
<td>2-16</td>
<td>3</td>
<td>Transient gastrointestinal disturbances</td>
<td>Titrate carefully in renal or hepatic dysfunction</td>
</tr>
<tr>
<td>Nateglinide</td>
<td></td>
<td>4</td>
<td>360</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Slow hydrolysis and absorption of complex carbohydrates</td>
<td>150-300</td>
<td>3 (with meals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td></td>
<td>150-300</td>
<td>3 (with meals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miglitol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Peripheral insulin sensitizer</td>
<td>4-8</td>
<td>1 or divided</td>
<td>Upper respiratory tract infection, headache, edema, weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>GLP-1 receptor agonist</td>
<td>24</td>
<td>50-100</td>
<td>1</td>
<td>Upper respiratory tract infection, sore throat, diarrhea</td>
<td>No data in children or adolescents</td>
</tr>
</tbody>
</table>


cells. They are occasionally used when metformin monotherapy is unsuccessful or contraindicated for some reason (use in certain forms of neonatal diabetes is discussed in the section on neonatal diabetes). Thiazolidinediones are not approved for use in pediatrics. Pramlintide (Symlin) is an analog of IAPP (islet amyloid polypeptide), which is a peptide that is cosecreted with insulin by the β cells and acts to delay gastric emptying, suppress glucagon, and possibly suppress food intake. It is not yet approved for pediatric use. Incretins are gut-derived peptides like GLP-1, GLP-2, and GIP (glucose-dependent insulinoanotropic peptide, previously known as gastric inhibitory protein) that are secreted in response to meals and act to enhance insulin secretion and action, suppress glucagon production, and delay gastric emptying (among other actions). GLP-1 analogs (e.g., exenatide) and agents that prolong endogenous GLP-1 action (e.g., sitagliptin) are now available for use in adults but are not yet approved for use in children; they may be associated with side effects such as hepatic injury and pancreatitis.

COMPLICATIONS

In the SEARCH study of diabetes in youth, 92% of the patients with T2DM had 2 or more elements of the metabolic syndrome (hypertension, hypertriglyceridemia, decreased high-density lipoprotein, increased waist circumference), including 70% with hypertension. In addition, the incidence of microalbuminuria and diabetic retinopathy appears to be higher in T2DM than it is in T1DM. In the SEARCH study, the incidence of microalbuminuria among patients who had T2DM of less than 5 yr duration was 7-22%, while retinopathy was present in 18.3%. Thus, all adolescents with T2DM should be screened for hypertension and lipid abnormalities and screening for microalbuminuria and retinopathy may be indicated even earlier than it is in T1DM. Sleep apnea and fatty liver disease are being diagnosed with increasing frequency and may necessitate referral to the appropriate specialists. Complications associated with all forms of diabetes and recommendations for screening are noted in Table 589-12; Table 589-15 lists additional conditions particularly associated with T2DM.

PREVENTION

The difficulties in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for T2DM, which is clearly linked to modifiable risk factors (obesity, a sedentary lifestyle). The Diabetes Prevention Program was designed to prevent or delay the development of T2DM in adult individuals at high risk by virtue of IGT. The Diabetes Prevention Program results demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of T2DM. The results were striking. Lifestyle intervention reduced the diabetes incidence by 58%; metformin reduced the incidence by 31% compared with placebo. The effects were similar for men and women and for all racial and ethnic groups. Lifestyle interventions are believed to have similar beneficial effects in obese adolescents with IGT. Screening is indicated for at-risk patients (see Table 589-13).
589.4 Other Specific Types of Diabetes
Britta M. Svoren and Nicholas Jospe

Most cases of diabetes in children as well as adults fall into the 2 broad categories of type 1 and type 2 diabetes, but up to 4% of cases are caused by single-gene disorders. These disorders include hereditary defects of β-cell function and insulin action, as well as rare forms of mitochondrial diabetes.

GENETIC DEFECTS OF B-CELL FUNCTION
Maturity-Onset Diabetes of Youth
Several forms of diabetes are associated with monogenic defects in β-cell function. Before these genetic defects were identified, this subset of diabetics was diagnosed on clinical grounds and described by the term MODY. This subtype of DM consists of a group of heterogeneous clinical entities that are characterized by onset before 25 yr, autosomal dominant inheritance, and a primary defect in insulin secretion. Strict criteria for the diagnosis of MODY include diabetes in at least 3 generations with autosomal dominant transmission and diagnosis before age 25 yr in at least 1 affected subject. Mutations have been found in at least 10 different genes, accounting for the dominantly inherited monogenic defects of insulin secretion, for which the term MODY is used. The American Diabetes Association groups these disorders together under the broader category of “genetic defects of β-cell function.” Eleven of these defects typically meet the clinical criteria for the diagnosis of MODY and are listed in Table 589-16. Just 3 of them (MODY2 and MODY3 and MODY5) account for 90% of the cases in this category in European populations, but the distribution may be different in other ethnic groups. Except for MODY2 (which is caused by mutations in the enzyme glucokinase), all other forms are caused by genetic defects in various transcription factors (Table 589-16).

MODY2
This is the second most common form of MODY and accounts for approximately 15-30% of all patients diagnosed with MODY. Glucokinase plays an essential role in β-cell glucose sensing and heterozygous mutations in this gene lead to mild reductions in pancreatic β-cell response to glucose. Homozygotes with the same mutations are completely unable to secrete insulin in response to glucose and develop a form of permanent neonatal diabetes. Patients with heterozygous mutations have a higher threshold for insulin release but are able to secrete insulin adequately once blood glucose rises above 7 mmol/L. This results in a relatively mild form of diabetes (HbA1c is usually less than 7%), with mild fasting hyperglycemia and IGT in the majority of patients. MODY2 may be misdiagnosed as type 1 diabetes in children, gestational diabetes in pregnant women, or well-controlled type 2 diabetes in adults (Table 589-17). An accurate diagnosis is important because most cases are not progressive, and except for gestational diabetes, may not require treatment. When needed, they can usually be treated with small doses of exogenously administered insulin. Treatment with oral agents (sulfonylureas and related drugs) can be successful and may be more acceptable to many patients.

MODY3
Patients affected with mutations in the transcription factor hepatocyte nuclear factor-1α show abnormalities of carbohydrate metabolism varying from IGT to severe diabetes and often progressing from a mild to a severe form over time. They are also prone to the development of vascular complications. This is the most common MODY subtype and accounts for 50-65% of all cases. These patients are very sensitive to the action of sulfonylureas and can usually be treated with relatively low doses of these oral agents, at least in the early stages of the disease. In children, this form of MODY is sometimes misclassified as T1DM and treated with insulin. Evaluation of autoimmune markers will rule out T1DM, and genetic testing for this form of MODY is now available and is indicated in patients with relatively mild diabetes and a family history suggestive of autosomal dominant inheritance. On the other hand, even patients with relatively mild and gradual onset of diabetes may have T1DM, and in the absence of a family history suggestive of autosomal dominant inheritance, the diagnosis of MODY is not warranted. Accurate diagnosis can lead to avoidance of unnecessary insulin treatment and specific genetic counseling.

Hepatocyte nuclear factor-4α (MODY1), insulin promoter factor (IPF)-1, also known as (PDX-1) (MODY4), hepatocyte nuclear factor 1β/TCF2 (MODY5), and NeuroD1 (MODY6) are all transcription factors that are involved in β-cell development and function and mutations in these lead to various rare forms of MODY. In addition to diabetes they can also have specific findings unrelated to hyperglycemia; for example, MODY1 is associated with low triglyceride and lipoprotein levels and MODY5 is associated with renal cysts and renal dysfunction. In terms of treatment, MODY1 and MODY4 may respond to oral sulfonylureas, but MODY5 does not respond to oral agents and requires treatment with insulin. NeuroD1 defects are extremely rare and not much is known about their natural history.

Primary or secondary defects in the glucose transporter-2, which is an insulin-independent glucose transporter, may also be associated with diabetes. Diabetes may also be a manifestation of a polymorphism in the glycogen synthase gene. This enzyme is crucially important for storage of glucose as glycogen in muscle. Patients with this defect are notable for marked insulin resistance and hypertension, as well as a strong family history of diabetes.

Mitochondrial Gene Defects
Maternally Inherited Diabetes and Deafness. Point mutations in mitochondrial DNA are sometimes associated with maternally inherited DM and deafness. The most common mitochondrial DNA mutation in these cases is the point mutation m.3243A>G in the transfer RNA leucine gene. This mutation is identical to the
Table 589-16 | Summary of MODY Types and Special Clinical Characteristics

<table>
<thead>
<tr>
<th>GENE MUTATED</th>
<th>FUNCTION</th>
<th>SPECIAL FEATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY1</td>
<td>HNF4α</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>MODY2</td>
<td>Glucokinase (GCK)</td>
<td>Enzyme, glucose sensor</td>
</tr>
<tr>
<td>MODY3</td>
<td>HNF1α</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>MODY4</td>
<td>IPF-1</td>
<td>Necessary for pancreatic development</td>
</tr>
<tr>
<td>MODY5</td>
<td>HNF1β</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>MODY6</td>
<td>NEUROD1</td>
<td>Differentiation factor in the development of pancreatic islets</td>
</tr>
<tr>
<td>MODY7</td>
<td>KFL11</td>
<td>Zinc finger transcription factor</td>
</tr>
<tr>
<td>MODY8</td>
<td>CEL</td>
<td>Bile salt–dependent lipase</td>
</tr>
<tr>
<td>MODY9</td>
<td>PAX4</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>MODY10</td>
<td>INS</td>
<td>Insulin gene</td>
</tr>
<tr>
<td>MODY11</td>
<td>BLK</td>
<td>B-lymphocyte tyrosine kinase</td>
</tr>
</tbody>
</table>

MODY, maturity-onset diabetes of the young.


Table 589-17 | Clinical and Biochemical Features Associated with Type 1 Diabetes, Type 2 Diabetes and the Common Subtypes of Maturity-Onset Diabetes of the Young

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>TYPE 1 DIABETES</th>
<th>TYPE 2 DIABETES</th>
<th>GCK-MODY</th>
<th>HNF1A/4A-MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age of diagnosis (yr)</td>
<td>10-30</td>
<td>&gt;25</td>
<td>Present from birth; presents at any age</td>
<td>15-45</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Parental history of diabetes</td>
<td>&lt;15%</td>
<td>&gt;50% in young onset type 2 diabetes</td>
<td>If tested, 1 parent usually has impaired fasting glycemia (may not be previously known)</td>
<td>60-90%*</td>
</tr>
<tr>
<td>Obesity</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Presence of β-cell antibodies</td>
<td>&gt;90%</td>
<td>Negative</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>C-peptide concentrations</td>
<td>Undetectable/low</td>
<td>Normal/high</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Optimal first-line treatment</td>
<td>Insulin</td>
<td>Metformin</td>
<td>None</td>
<td>Sulfonlurea</td>
</tr>
</tbody>
</table>

*Family history is often part of the criteria for testing. Some reports cite a parental history of 60-70%.

GCK, glucokinase; HNF1A/4A, hepatocyte nuclear factor 1α/4α; MODY, maturity-onset diabetes of the young.

From Thanabalasingham G, Owen KR: Diagnosis and management of maturity onset diabetes of the young (MODY), BMJ 343:d6044, 2011, Table 2, p. 838.

mutation in MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome), but this syndrome is not associated with diabetes; the phenotypic expression of the same defect varies. Diabetes in most of these cases presents insidiously but approximately 20% of patients have an acute presentation resembling T1DM. The mean age of diagnosis of diabetes is 37 yr but cases have been reported as young as 11 yr. This mutation has been estimated to be present in 1.5% of Japanese diabetics, which may be higher than the prevalence in other ethnic groups. Metformin should be avoided in these patients because of the theoretical risk of severe lactic acidosis in the presence of mitochondrial dysfunction.

Another form of IDDM, sometimes associated with mitochondrial mutations, is the Wolfram syndrome. Wolfram syndrome 1 is characterized by diabetes insipidus, DM, optic atrophy, and deafness—thus, the acronym DIDMOAD. Some patients with diabetes appear to have severe insulinopenia, whereas others have significant insulin secretion as judged by C-peptide. The overall prevalence is 1 in 770,000 live births. The sequence of appearance of the stigmata is as follows: non-autoimmune IDDM in the 1st decade, central diabetes insipidus and sensorineural deafness in two thirds to three fourths of the patients in the 2nd decade, renal tract anomalies in about one half of the patients in the 3rd decade, and neurologic complications such as cerebellar ataxia and myoclonus in one half to two thirds of the patients in the 4th decade. Other features include primary gonadal atrophy in the majority of males and a progressive neurodegenerative course with neurorespiratory death at a median age of 30 yr. Some (but not all) cases are caused by mutations in the WFS-1 (wolframin) gene on chromosome 4p. Wolfram syndrome 2 has early-onset optic atrophy, DM, deafness, and a shortened life span but no diabetes insipidus; the associated gene is CISD2.
DIABETES MELLITUS OF THE NEWBORN

Neonatal DM is exceedingly rare. Onset of classic autoimmune T1DM before the age of 6 mo is most unusual and most cases of diabetes in this age range are caused by genetic mutations.

Transient Neonatal Diabetes Mellitus

Neonatal diabetes is transient in approximately 50% of cases, but after an interim period of normal glucose tolerance, 50–60% of these patients develop permanent diabetes (at an average age of 14 yr). There are also reports of patients with classic T1DM who formerly had transient diabetes of the newborn. It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classic T1DM is a chance occurrence or causally related.

The syndrome of transient DM in the newborn infant has its onset in the 1st wk of life and persists several weeks to months before spontaneous resolution. Median duration is 12 wk. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and, at times, metabolic acidosis, but with only minimal or no ketonemia or ketonuria. There may also be findings such as umbilical hernia or large tongue. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations are normal. After spontaneous recovery, the insulin responses to these same stimuli are brisk and normal, implying a functional delay in β-cell maturation with spontaneous resolution. Occurrence of the syndrome in consecutive siblings has been reported. About 70% of cases are due to abnormalities of an imprinted locus on chromosome 6q24, resulting in overexpression of paternally expressed genes such as pleomorphic adenoma gene—like 1 (PLAG1/ZAC) and hydridiform mole—associated imprinted (HYMA1). Most of the remaining cases are caused by mutations in Kir6.2 channels. Mutations in Kir6.2 channels also cause many cases of permanent neonatal diabetes, but there is practically no overlap between the mutations that lead to transient neonatal DM and those causing permanent neonatal DM. This syndrome of transient neonatal DM should be distinguished from the severe hyperglycemia that may occur in hypotonic dehydration; that usually occurs in infants beyond the newborn period and responds promptly to rehydration with minimal or no requirement for insulin.

Administration of insulin is mandatory during the active phase of DM in the newborn. One to 2 units/kg/24 hr of an intermediate—acting insulin in 2 divided doses usually results in dramatic improvement and accelerated growth and gain in weight. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifest or after 2 mo of age. Genetic testing is now available for 6q24 abnormalities as well as potassium channel defects and should be obtained on all patients and recurrence risk assessment by a genetic counselor is recommended.

Permanent Neonatal Diabetes Mellitus

Permanent DM in the newborn period is caused in approximately 50% of the cases by mutations in the KCNJ11 (potassium inwardly-rectifying channel J, member 11) and ABCC8 (adenosine triphosphate—binding cassette, subfamily C, member 8) genes. These genes code for the Kir6.2 and SUR1 subunits of the adenosine triphosphate—sensitive potassium channel, which is involved in an essential step in insulin secretion at the β cell. Some cases are caused by pancreatic agenesis as a result of homozygous mutations in the IPF1 gene (where heterozygous mutations cause MODY4); homozygous mutations in the glucokinase gene (where heterozygous mutations cause MODY2); and mutations in the insulin gene. Almost all these infants are small at birth because of the role of insulin as an intrauterine growth factor. Instances of affected twins and families with more than 1 affected infant have been reported. Infants with permanent neonatal DM may be initially euglycemic and typically present between birth and 6 mo of life (mean age of presentation is 5 wk). There is a spectrum of severity and up to 20% have neurologic features. The most severely affected patients have the syndrome of developmental delay, epilepsy and neonatal diabetes (DEND syndrome). Less-severe forms of DEND are labeled intermediate DEND or i-DEND.

Activating mutations in the KCNJ11 gene (encoding the adenosine triphosphate—sensitive potassium channel subunit Kir6.2) are associated with both transient neonatal DM and permanent neonatal DM, with particular mutations being associated with each phenotype. More than 90% of these patients respond to sulfonylureas (at higher doses than those used in T2DM), but patients with severe neurologic disease may be less responsive. Mutations in the ABCC8 gene (encoding the SUR1 subunit of this potassium channel) were thought to be less likely to respond to sulfonylureas (because this is the subunit that binds sulfonylurea drugs), but some of these mutations are reported to respond and patients have been successfully switched from insulin to oral therapy. Several protocols for switching the patient from insulin to glibenclamide are available and patients are usually stabilized on doses ranging from 0.4–1 mg/kg/day. Because approximately 50% of neonatal diabetes have K-channel mutations that can be switched to sulfonylurea therapy, with dramatic improvement in glycemic control and quality of life, all patients with diabetes diagnosed before 6 mo of age (and perhaps even those diagnosed before 12 mo of age) should now be screened for these mutations by genetic testing.

IPEX Syndrome

IPEX means immunodysregulation, polyendocrinopathy, and enteropathy, X—linked. In most patients with IPEX, mutations in the FOXP3 (Forkhead box P3) gene, a specific marker of natural and adaptive regulatory T cells, leads to severe immune dysregulation and rampant autoimmunity. Autoimmune diabetes develops in >90% of cases, usually within the 1st few wk of life and is accompanied by enteropathy, failure to thrive, and other autoimmune disorders (see Chapter 126.5).

Abnormalities of the Insulin Gene

Diabetes of variable degrees may also result from defects in the insulin gene that lead to various amino acid substitutions that impair the effectiveness of insulin at the receptor level. Insulin gene defects are exceedingly rare and may be associated with relatively mild diabetes or even normal glucose tolerance. Diabetes may also develop in patients with faulty processing of proinsulin to insulin (an autosomal dominant defect). These defects are notable for the high concentration of insulin as measured by radioimmunoassay, whereas MODY and glucose transporter—2 defects are characterized by relative or absolute deficiency of insulin secretion for the prevailing glucose concentrations.

GENETIC DEFECTS OF INSULIN ACTION

Various genetic mutations in the insulin receptor can impair the action of insulin at the insulin receptor or impair postreceptor signaling, leading to insulin resistance.

The mildest form of the syndrome with mutations in the insulin receptor was previously known as type A insulin resistance. This is associated with hirsutism, hyperandrogenism, and cystic ovaries in females, without obesity. Acanthosis nigricans may be present and life expectancy is not significantly impaired. More-severe forms of insulin resistance are seen in 2 mutations in the insulin receptor gene that cause the pediatric syndromes of Donohue syndrome (formerly called leprechaunism) and Rabson-Mendenhall syndrome.

Donohue Syndrome

This is a syndrome characterized by intrauterine growth restriction, fasting hypoglycemia, and postprandial hyperglycemia in association with profound resistance to insulin; severe hyperinsulinemia is seen compared to age—matched infants during an oral glucose tolerance test. Various defects of the insulin receptor have been described, thereby attesting to the important role of insulin and its receptor in fetal growth and possibly in morphogenesis. Most of these patients die in the 1st yr of life.

Rabson-Mendenhall Syndrome

This entity is defined by clinical manifestations that appear to be intermediate between those of acanthosis nigricans with insulin resistance type A and Donohue syndrome. The features include extreme insulin
Clinical and Biochemical Features of Inherited Lipodystrophies

<table>
<thead>
<tr>
<th>Subtype</th>
<th>CONGENITAL GENERALIZED LIPODYSTROPHY</th>
<th>FAMILIAL PARTIAL LIPODYSTROPHY</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>BSCL1</td>
<td>BSCL2</td>
</tr>
<tr>
<td>Defective gene</td>
<td>AGPAT2</td>
<td>BSCL2</td>
</tr>
<tr>
<td>Clinical onset</td>
<td>Soon after birth</td>
<td>Soon after birth</td>
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<tr>
<td>Fat distribution</td>
<td>Generalized absence</td>
<td>Generalized absence</td>
</tr>
<tr>
<td>Cutaneous features</td>
<td>Acanthosis nigricans and skin tags; hirsutism common in women</td>
<td>Acanthosis nigricans and skin tags; hirsutism common in women</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Acromegaloid features common</td>
<td>Acromegaloid features common</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Severe associated with pancreatitis</td>
<td>Severe associated with pancreatitis</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Severe early onset</td>
<td>Severe early onset</td>
</tr>
<tr>
<td>Diabetes onset</td>
<td>&lt;20 yr</td>
<td>&lt;20 yr</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Other</td>
<td>Mild mental retardation possible</td>
<td></td>
</tr>
</tbody>
</table>


resistance, acanthosis nigricans, abnormalities of the teeth and nails, and pineal hyperplasia. It is not clear whether this syndrome is entirely distinct from Donohue syndrome; however, by comparison, patients with Rabson-Mendenhall tend to live significantly longer. Therapies with modest benefit have included insulin-like growth factor-1 and leptin.

Lipoatrophic Diabetes
Various forms of lipodystrophy are associated with insulin resistance and diabetes (Table 589-18). Familial partial lipodystrophy is associated with mutations in the LMNA gene, encoding nuclear envelope proteins lamin A and C. Severe generalized lipodystrophy is associated with mutations in the seipin and LMNA genes, but the mechanism by which these mutations lead to insulin resistance and diabetes is not known.

Stiff-Person Syndrome
This is an extremely rare autoimmune central nervous system disorder that is characterized by progressive stiffness and painful spasms of the axial muscles and very high titers of glutamic acid decarboxylase antibodies. About one third of the patients also develop T1DM.

Systemic Lupus Erythematosus
In rare cases, patients with systemic lupus erythematosus may develop autoantibodies to the insulin receptor, leading to insulin resistance and diabetes.

Cystic Fibrosis–Related Diabetes
See Chapter 403.

As patients with cystic fibrosis (CF) live longer, an increasing number are being diagnosed with cystic fibrosis–related diabetes (CFRD). Females appear to have a somewhat higher risk of CFRD than males and prevalence increases with increasing age until age 40 yr (there is a decline in prevalence after that, presumably because only the healthiest CF patients survive beyond that age). There is an association with pancreatic insufficiency and there may be a higher risk in patients with class I and class II CF transmembrane conductance regulator mutations. A large multicenter study in the United States reported prevalence (in all ages) of 17% in females and 12% in males. Cross-sectional studies indicate that the prevalence of IGT may be significantly higher than this and up to 65% of children with CF have diminished 1st phase insulin secretion, even when they have normal glucose tolerance. In Denmark, oral glucose tolerance screening of the entire CF population demonstrated no diabetes in patients younger than 10 yr; diabetes in 12% of patients age 10-19 yr, and diabetes in 48% of adults age 20 yr and older. At a Midwestern center where routine annual oral glucose tolerance screening is performed, only about one half of children and one fourth of adults have normal glucose tolerance.

Patients with CFRD have features of both T1DM and T2DM. In the pancreas, exocrine tissue is replaced by fibrosis and fat and many of the pancreatic islets are destroyed. The remaining islets demonstrate diminished numbers of β-, α-, and pancreatic polypeptide-secreting cells. Secretion of the islet hormones insulin, glucagon, and pancreatic polypeptide is impaired in patients with CF in response to a variety of secretagogues. This pancreatic damage leads to slowly progressive insulin deficiency, of which the earliest manifestation is an impaired 1st phase insulin response. As patients age, this response becomes progressively delayed and less robust than normal. At the same time, these patients develop insulin resistance due to chronic inflammation and the intermittent use of corticosteroids. Insulin deficiency and insulin resistance lead to a very gradual onset of IGT that eventually evolves into diabetes. In some cases, diabetes may wax and wane with disease exacerbations and the use of corticosteroids. The clinical presentation is similar to that of T2DM in that the onset of the disease is insidious and the occurrence of ketoacidosis is rare. Islet antibody titers are negative. Microvascular complications do develop but may do so at a slower rate than in typical T1DM or T2DM. Macrovascular complications do not appear to be of concern in CFRD, perhaps because of the shortened
life span of these patients. Several factors unique to CF influence the onset and the course of diabetes. For example: (1) frequent infections are associated with waxing and waning of insulin resistance; (2) energy needs are increased because of infection and pulmonary disease; (3) malabsorption is common, despite enzyme supplementation; (4) nutrient absorption is altered by abnormal intestinal transit time; (5) liver disease is frequently present; (6) anorexia and nausea are common; (7) there is a wide variation in daily food intake based on the patient’s acute health status; and (8) both insulin and glucagon secretion are impaired (in contrast to autoimmune diabetes, in which only insulin secretion is affected).

Impaired glucose tolerance and CFRD are associated with poor weight gain and there is evidence that treatment with insulin improves weight gain and slows the rate of pulmonary deterioration. Because of these observations, the CF Foundation recommends routine diabetes screening of all children with CF, starting at age 12 yr. Despite debate over the ideal screening modality, the current recommendation is the 2 hr glucose tolerance test, though it is possible that simply obtaining a single 2 hr postprandial glucose value may be sufficient. When hyperglycemia develops, the accompanying metabolic derangements are usually mild, and relatively low doses of insulin usually suffice for adequate management. Basal insulin may be started initially, but basal-bolus therapy similar to that used in T1DM will eventually be needed. Dietary restrictions are minimal as increased energy needs are present and weight gain is usually desired. Ketoadiposis is very uncommon but may occur with progressive deterioration of islet cell function. Impaired glucose tolerance is not necessarily an indication for treatment, but patients who have poor growth and inadequate weight gain may benefit from the addition of basal insulin even if they do not meet the criteria for diagnosis of diabetes.

AUTOIMMUNE DISEASES

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is frequently associated with T1DM in children (see Chapter 566). As many as 1 in 5 insulin-dependent diabetic patients have thyroid antibodies in their serum; the prevalence is 2-20 times greater than in control populations. Only a small proportion of these patients, however, acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 yr. Periodic palpation of the thyroid gland is indicated in all diabetic children; if the gland feels firm or enlarged, serum measurements of thyroid antibodies and TSH should be obtained. A confirmed TSH level of greater than 10 µU/mL indicates existing or incipient thyroid dysfunction that warrants replacement with thyroid hormone. Deceleration in the rate of growth may also be caused by thyroid failure and is, in itself, a reason for securing serum measurements of thyroxine and TSH concentrations.

When diabetes and thyroid disease coexist, the possibility of autoimmune adrenal insufficiency should be considered. It may be heralded by decreasing insulin requirements, increasing pigmentation of the skin and buccal mucosa, salt craving, weakness, asthenia and postural hypotension, or even frank Addisonian crisis. This syndrome is most unusual in the 1st decade of life, but it may become apparent in the 2nd decade or later.

Celiac disease, which is caused by hypersensitivity to dietary gluten, is another autoimmune disorder that occurs with significant frequency in children with T1DM (see Chapter 338.2). It is estimated that approximately 7-15% of children with T1DM develop celiac disease within the 1st 6 yr of diagnosis, and the incidence of celiac disease is significantly higher in children younger than 4 yr of age and in girls. Young children with T1DM and celiac disease usually present with gastrointestinal symptoms (abdominal cramping, diarrhea, and gastrointestinal reflux), growth failure as a consequence of suboptimal weight gain, and unexplained hypoglycemic reactions because of nutrient malabsorption, including vitamin D; adolescents may remain asymptomatic. The diagnosis of celiac disease is considered if serum tissue transglutaminase antibody titers are elevated in the presence of normal serum total IgA levels. The diagnosis is confirmed on endoscopic evaluation and biopsy of small bowel revealing characteristic atrophy of intestinal villi. Therapy consists of a gluten-free diet, which will alleviate gastrointestinal symptoms and may reduce glycemic excursions.

Circulating antibodies to gastric parietal cells and to intrinsic factor are 2-3 times more common in patients with T1DM than in control subjects. The presence of antibodies to gastric parietal cells is correlated with atrophic gastritis and antibodies to intrinsic factor are associated with malabsorption of vitamin B₁₂. However, megaloblastic anemia is rare in children with T1DM.

A variant of the multiple endocrine deficiency syndrome is characterized by T1DM, idiopathic intestinal mucosal atrophy with associated inflammation and severe malabsorption, IgA deficiency, and circulating antibodies to multiple endocrine organs including the thyroid, adrenal, pancreas, parathyroid, and gonads. In addition, non-diabetic family members have an increased frequency of vitiligo, Graves disease, and multiple sclerosis as well as low complement levels and antibodies to endocrine tissues.

ENDOCRINOPATHIES

The endocrinopathies listed in Table 589-1 are only rarely encountered as a cause of diabetes in childhood. They may accelerate the manifestations of diabetes in those with inherited or acquired defects in insulin secretion or action.

DRUGS

High-dose oral or parenteral steroid therapy usually results in significant insulin resistance leading to glucose intolerance and overt diabetes. The immunosuppressive agents cyclosporin and tacrolimus are toxic to β cells, causing IDDM in a significant proportion of patients treated with these agents. Their toxicity to pancreatic β cells was 1 of the factors that limited their usefulness in arresting ongoing autoimmune destruction of β cells. Streptozotocin and the rodenticide Vacor are also toxic to β cells, causing diabetes.

There are no consensus guidelines regarding treatment of steroid-induced hyperglycemia in children. Many patients on high-dose steroids have elevated blood glucose during the day and evening, but become normoglycemic late at night and early in the morning. In general, significant hyperglycemia in an inpatient setting is treated with short-acting insulin on an as-needed basis. Basal insulin may be added when fasting hyperglycemia is significant. Outpatient treatment can be more difficult, but when treatment is needed, protocols similar to the basal-bolus regimens used in T1DM are used.

GENETIC SYNDROMES ASSOCIATED WITH DIABETES MELLITUS

A number of rare genetic syndromes associated with IDDM or carbohydrate intolerance have been described (see Table 589-1). These syndromes represent a broad spectrum of diseases, ranging from premature cellular aging, as in the Werner and Cockayne syndromes (see Chapter 90) to excessive obesity associated with hyperinsulinism, resistance to insulin action, and carbohydrate intolerance, as in the Prader-Willi syndrome (see Chapters 80 and 81). Some of these syndromes are characterized by primary disturbances in the insulin receptor or in antibodies to the insulin receptor without any impairment in insulin secretion. Although rare, these syndromes provide unique models to understand the multiple causes of disturbed carbohydrate metabolism from defective insulin secretion or from defective insulin action at the cell receptor or postreceptor level.

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HISTORY
A detailed history is the cornerstone of any neurologic assessment. Although parents may be the primary informants, most children older than 3-4 yr are capable of contributing to their history and should be questioned directly.

The history should begin with the chief complaint, as well as a determination of the complaint's relative significance within the context of normal development (see Chapters 9-16). The latter step is critical because a 13 mo old who cannot walk may be perfectly normal, whereas a 4 yr old who cannot walk might have a serious neurologic condition.

Next, the history of present illness should provide a chronological outline of the patient's symptoms, with attention paid to location, quality, intensity, duration, associated features, and alleviating or exacerbating factors. It is essential to perform a review of systems, because abnormalities of the central nervous system (CNS) often manifest with vague, nonfocal symptoms that may be misattributed to other organ systems (e.g., vomiting, constipation, urinary incontinence). A detailed history might suggest that vomiting is as a result of increased intracranial pressure (ICP) rather than gastritis or that constipation and urinary incontinence are caused by a spinal cord tumor rather than behavioral stool withholding. In addition, a systemic illness may produce CNS manifestations such as lupus erythematosus (seizures, psychosis, demyelination) or mitochondrial disorders (developmental delay, strokes, hypotonia).

Following the chief complaint and history of present illness, the physician should obtain a complete birth history, particularly if a congenital disorder is suspected. The birth history should begin with a review of the pregnancy, including specific questions about common complications, such as pregnancy-induced hypertension, preclampsia, gestational diabetes, vaginal bleeding, infections, and falls. It is important to quantify any cigarette, alcohol, or drug (prescription, herbal, illicit) use. Inquiring about fetal movement might provide clues to an underlying diagnosis, because decreased or absent fetal activity can be associated with chromosomal anomalies and CNS or neuromuscular disorders. Finally, any abnormal ultrasound or amniocentesis results should be noted.

A labor history should address the gestational age at delivery and mode of delivery (spontaneous vaginal, vacuum- or forceps-assisted, cesarean section) and should comment on the presence or absence of fetal distress. If delivery was by cesarean section, it is essential to record the indication for surgery.

The birth weight, length, and head circumference provide useful information about the duration of a given problem, as well as insights into the uterine environment. Parents can usually provide a reliable history of their child's postnatal course; however, if the patient was resuscitated or had a complicated hospital stay, it is often helpful to obtain the hospital records. The physician should inquire about the infant's general well-being, feeding and sleeping patterns, activity level, and the nature of the infant's cry. If the infant had jaundice, it is important to determine both the degree of jaundice and how it was managed.

Historical markers of neurologic dysfunction include full-term infants who are unable to breathe spontaneously; have poor, uncoordinated sucks; need an inordinate amount of time to feed; or require gavage feeding. Again, it is important to consider the developmental context, because all of these issues would be expected in premature infants, particularly those with a very-low birthweight. Double-checking the state newborn screening results may provide a clue to abnormal neurologic manifestation in an infant.

The most important component of a neurologic history is the developmental assessment (see Chapters 9-14 and 16). Careful evaluation of a child's social, cognitive, language, fine motor, and gross motor skills is required to distinguish normal development from either isolated or global (i.e., in 2 or more domains) developmental delay. An abnormality in development from birth suggests an intrauterine or perinatal cause, but a loss of skills (regression) over time strongly suggests an underlying degenerative disease of the CNS, such as an inborn error of metabolism. The ability of parents to recall the precise timing of their child's developmental milestones is extremely variable. It is often helpful to request old photographs of the child or to review the baby book, where the milestones may have been dutifully recorded. In general, parents are aware when their child has a developmental problem, and the physician should show appropriate concern. Table 590-1 outlines the upper limits of normal for attaining specific developmental milestones. Chapter 16 includes a comprehensive review of developmental screening tests and their interpretation.

Family history is extremely important in the neurologic evaluation of a child. Most parents are extremely cooperative in securing medical information about family members, particularly if it might have relevance for their child. The history should document the age and history of neurologic disease, including developmental delay, epilepsy, migraine, stroke, and inherited disorders, for all 1st- and 2nd-degree relatives. It is important to inquire directly about miscarriages or fetal deaths in utero and to document the sex of the embryo or fetus, as well as the gestational age at the time of demise. When available, the results of postmortem examinations should be obtained, as they can have a direct bearing on the patient's condition. The parents should be questioned about their ethnic backgrounds, because some genetic disorders occur more commonly within specific populations (e.g., Tay-Sachs disease in the Ashkenazi Jewish population). They should also be asked if there is any chance that they could be related to each other, because the incidence of metabolic and degenerative disorders of the CNS is increased significantly in children of consanguineous marriages.

The social history should detail the child's current living environment, as well as the child's relationship with other family members. It is important to inquire about recent stressors, such as divorce, remarriage, birth of a sibling, or death of a loved one, because they can affect the child's behavior. If the child is in daycare or school, one should document the child's academic and social performance, paying particular attention to any abrupt changes. Academic performance can be assessed by asking about the child's latest report card, and peer relationships can be evaluated by having the child name his or her "best friends." Any child who is unable to name at least 2 or 3 playmates might have abnormal social development. In some cases, discussions with the daycare worker or teacher provide useful ancillary data.

NEUROLOGIC EXAMINATION
The neurologic examination begins at the outset of the interview. Indirect observation of the child's appearance and movements can yield valuable information about the presence of an underlying disorder. For instance, it may be obvious that the child has dysmorphic facies, an
unusual posture, or an abnormality of motor function manifested by a hemiparesis or gait disturbance. The child's behavior while playing and interacting with his or her parents may also be telling. A normal child usually plays independently early in the visit, but then engages in the interview process. A child with attention-deficit/hyperactivity disorder might display impulsive behavior in the examining room, and a child with neurologic impairment might exhibit complete lack of awareness of the environment. Finally, note should be made of any unusual odors about the patient, because some metabolic disorders produce characteristic scents (e.g., the “musty” smell of phenylketonuria or the “sweaty feet” smell of isovaleric acidemia). If such an odor is present, it is important to determine whether it is persistent or transient, occurring only with illnesses.

The examination should be conducted in a nonthreatening, child-friendly setting. The child should be allowed to sit where the child is most comfortable, whether it be on a parent's lap or on the floor of the examination room. The physician should approach the child slowly, reserving any invasive or painful tests (e.g., measurement of head circumference, gag reflex) for the end of the examination. In the end, the more that the examination seems like a game, the more the child will cooperate. Because the neurologic examination of an infant requires a somewhat modified approach from that of an older child, the 2 groups are considered separately (see Chapters 9, 10, and 94 vs Chapters 11-14).

Mental Status
Age aside, the neurologic examination should include an assessment of the patient's mental status in terms of both level of arousal and interaction with the environment. Premature infants born at <28 wk of gestation do not have consistent periods of alertness, whereas slightly older infants arouse from sleep with gentle physical stimulation. Sleep–wake patterns are well developed at term. Because the level of alertness of a neonate depends on many factors, including the time of the last feeding, room temperature, and gestational age, serial examinations are critical when evaluating for changes in neurologic function. Older children's mental status can be assessed by watching them play. Having them tell a story, draw a picture, or complete a puzzle can also be helpful in assessing cognitive function. Memory can be evaluated informally as patients recount their personal information, as well as more formally by asking them to register and recall 3 objects or perform a digit span.

Head
Correct measurement of the head circumference is important. It should be performed at every visit for patients younger than 3 yr and should be recorded on a suitable head growth chart. To measure, a nondistensible plastic measuring tape is placed over the mid-forehead and extended circumferentially to include the most prominent portion of the occiput. If the patient's head circumference is abnormal, it is important to document the head circumferences of the parents and siblings. Errors in the measurement of a newborn skull are common owing to scalp edema, overriding sutures, and the presence of cephalohematomas. The average rate of head growth in a healthy premature infant is 0.5 cm in the 1st 2 wk, 0.75 cm in the 3rd wk, and 1.0 cm in the 4th wk and every week thereafter until the 40th wk of development. The head circumference of an average term infant measures 34-35 cm at birth, 44 cm at 6 mo, and 47 cm at 1 yr of age (see Chapters 9 and 10).

If the brain is not growing, the skull will not grow; therefore, a small head frequently reflects a small brain, or microcephaly. Conversely, a large head may be associated with a large brain, or macrocephaly, which is most commonly familial but may be from a disturbance of growth, neurocutaneous disorder (e.g., neurofibromatosis), chromosomal defect (e.g., Klinefelter syndrome), or storage disorder. Alternatively, the head size may be increased secondary to hydrocephalus (Fig. 590-1) or chronic subdural hemorrhages. In the latter case, the skull tends to assume a square or box-like shape, because the long-standing presence of fluid in the subdural space causes enlargement of the middle fossa.

The shape of the head should be documented carefully. Plagiocephaly, or flattening of the skull, can be seen in normal infants but may be particularly prominent in hypotonic or weak infants, who are less mobile. A variety of abnormal head shapes can be seen when cranial sutures fuse prematurely, as in the various forms of inherited craniosynostosis (see Chapter 591.12).

An infant has 2 fontanels at birth: a diamond-shaped anterior fontanel at the junction of the frontal and parietal bones that is open at birth, and a triangular posterior fontanel at the junction of the parietal and occipital bones that can admit the tip of a finger or may be closed at birth. If the posterior fontanel is open at birth, it should close over the ensuing 6-8 wk; its persistence suggests underlying hydrocephalus or congenital hypothyroidism. The anterior fontanel varies greatly in size, but it usually measures approximately 2 × 2 cm. The average time of closure is 18 mo, but the fontanel can close normally as early as 9 mo. A very small or absent anterior fontanel at birth might indicate craniosynostosis or microcephaly, whereas a very large fontanel can

### Table 590-1  | Screening Scheme for Developmental Delay: Upper Range

<table>
<thead>
<tr>
<th>AGE (mo)</th>
<th>GROSS MOTOR</th>
<th>FINE MOTOR</th>
<th>SOCIAL SKILLS</th>
<th>LANGUAGE</th>
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<tbody>
<tr>
<td>3</td>
<td>Supports weight on forearms</td>
<td>Opens hands spontaneously</td>
<td>Smiles appropriately</td>
<td>Coos, laughs</td>
</tr>
<tr>
<td>6</td>
<td>Sits momentarily</td>
<td>Transfers objects</td>
<td>Shows likes and dislikes</td>
<td>Babbles</td>
</tr>
<tr>
<td>9</td>
<td>Pulls to stand</td>
<td>Pincer grasp</td>
<td>Plays pat-a-cake, peek-a-boo</td>
<td>Imitates sounds</td>
</tr>
<tr>
<td>12</td>
<td>Walks with 1 hand held</td>
<td>Releases an object on command</td>
<td>Comes when called</td>
<td>1-2 meaningful words</td>
</tr>
<tr>
<td>18</td>
<td>Walks upstairs with assistance</td>
<td>Feeds from a spoon</td>
<td>Mimics actions of others</td>
<td>At least 6 words</td>
</tr>
<tr>
<td>24</td>
<td>Runs</td>
<td>Builds a tower of 6 blocks</td>
<td>Plays with others</td>
<td>2-3–word sentences</td>
</tr>
</tbody>
</table>

**Figure 590-1** Congenital hydrocephalus. Note the enlarged cranium and prominent scalp veins.
signify a variety of problems. The fontanel is normally slightly depressed and pulsatile and is best evaluated by holding the infant upright while the infant is asleep or feeding. A bulging fontanel is a potential indicator of increased ICP, but vigorous crying can cause a protuberant fontanel in a normal infant. Inspection of the head should include observation of the venous pattern, because increased ICP and thrombosis of the superior sagittal sinus can produce marked venous distention. Dysmorphic facial features can indicate a neurodevelopmental aberration. Likewise, cutaneous abnormalities, such as cutis aplasia or abnormal hair whorls, can suggest an underlying brain malformation or genetic disorder.

Palpation of a newborn's skull characteristically reveals molding of the skull accompanied by overriding sutures—a result of the pressures exerted on the skull during its descent through the pelvis. Marked overriding of the sutures beyond the early neonatal period is cause for alarm, because it suggests an underlying brain abnormality. Palpation additionally might reveal bony bridges between sutures (craniosynostosis), cranial defects, or, in premature infants, softening of the parietal bones (craniotabes).

Auscultation of the skull is an important adjunct to the neurologic examination. Cranial bruits may be noted over the anterior fontanel, temporal region, or orbits, and are best heard using the diaphragm of the stethoscope. Soft symmetric bruits may be discovered in normal children younger than 4 yr of age or in association with a febrile illness. Demonstration of a loud or localized bruit is usually significant and warrants further investigation, because they may be associated with severe anemia, increased ICP or arteriovenous malformations of the middle cerebral artery or vein of Galen. It is important to exclude murmurs arising from the heart or great vessels, because they may be transmitted to the cranium.

**Cranial Nerves**

**Olfactory Nerve (Cranial Nerve I)**

Anosmia, loss of smell, most commonly occurs as a transient abnormality in association with an upper respiratory tract infection or allergies. Permanent causes of anosmia include head trauma with damage to the ethmoid bone or shearing of the olfactory nerve fibers as they cross the cribiform plate, tumors of the frontal lobe, intranasal drug use, and exposure to toxins (acrylates, methacrylates, cadmium). Occasionally, a child who recovers from purulent meningitis or develops hydrocephalus has a diminished sense of smell. Rarely, anosmia is congenital, in which case it can occur as an isolated deficit or as part of Kalman syndrome, a familial disorder characterized by hypogonadotropic hypogonadism and congenital anosmia. Although not a routine component of the examination, smell can be tested reliably as early as the 32nd wk of gestation by presenting a stimulus and observing for an alerting response, withdrawal, or both. Care should be taken to use appropriate stimuli, such as coffee or peppermint, as opposed to strongly aromatic substances (e.g., ammonia inhalants) that stimulate the trigeminal nerve. Each nostril should be tested individually by pinching shut the opposite side.

**Optic Nerve (Cranial Nerve II)**

Assessment of the optic disc and retina is a critical component of the neurologic examination. Although the retina is best visualized by dilating the pupil, most physicians do not have ready access to mydriatic agents at the bedside; therefore, it may be necessary to consult an ophthalmologist in some cases. Mydriatics should not be administered to patients whose pupillary responses are being followed as a marker for impending herniation or to patients with cataracts. When mydriatics are used, both eyes should be dilated, because unilateral papillary fixation and dilation can cause confusion and worry in later examiners unaware of the pharmacologic intervention. Examination of an infant's retina may be facilitated by providing a nipple or soother and by turning the head to one side. The physician gently strokes the patient to maintain arousal, while examining the closer eye. An older child should be placed in the parent's lap and should be distracted by bright objects or toys. The color of the optic nerve is salmon-pink in a child but may be gray-white in a newborn, particularly if the newborn has fair coloring. This normal finding can cause confusion and can lead to the improper diagnosis of optic atrophy.

Disc edema refers to swelling of the optic disc, and papilledema specifically refers to swelling that is secondary to increased ICP. Papilledema rarely occurs in infancy because the skull sutures can separate to accommodate the expanding brain. In older children, papilledema may be graded according to the Frisen scale (Fig. 590-2). Disc edema must be differentiated from papillitis, or inflammation of the optic nerve. Both conditions manifest with enlargement of the blind spot, but visual acuity and color vision tend to be spared in early papilledema in contrast to what occurs in optic neuritis.

Retinal hemorrhages occur in 30-40% of all full-term newborn infants. The hemorrhages are more common after vaginal delivery than after Cesarean section and are not associated with birth injury or with neurologic complications. They disappear spontaneously by 1-2 wk of age. The presence of retinal hemorrhages beyond the early neonatal period should raise a concern for nonaccidental trauma.

**Vision**

At 28 wk of corrected gestational age, a premature infant blinks in response to a bright light, and at 32 wk, the infant maintains eye closure until the light source is removed. A normal 37 wk infant turns the head and eyes toward a soft light, and a term infant is able to fix on and follow a target, such as the examiner's face. Optokinetic nystagmus (OKN), which is conjugate nystagmus that occurs during attempted fixation on a series of rapidly moving objects, can also be used as a crude assessment of the visual system in infants. OKN is elicited by moving an OKN tape—usually a strip of material with alternating 2-inch black and white strips—across the patient's visual field. Although OKN responses can be tested monocularly in neonates, they do not become symmetric until 4-6 mo of age.

Visual fields can be tested in an infant or young child by advancing a brightly colored object from behind the patient's head into the peripheral visual field and noting when the patient first looks at the object. Suspension of the object by a string prevents the patient from focusing on the examiner's hand and arm. The examiner should be certain that the patient is responding to seeing, not hearing, the object.

Visual acuity in term infants approximates 20/150 and reaches the adult level of 20/20 by about 6 mo of age. Children who are too young to read the standard letters on a Snellen eye chart may learn the "E game," which entails pointing to indicate the direction that the E is facing. Children as young as 2.5-3 yr of age can identify the objects on a pediatric eye chart (Allen chart) at a distance of 15-20 ft.

The pupil reacts to light by 29-32 wk of corrected gestational age; however, the pupillary response is often difficult to evaluate, because premature infants resist eye opening and have poorly pigmented irises. Pupillary size, symmetry, and reactivity may be affected by drugs, space-occupying brain lesions, metabolic disorders, and abnormalities of the optic nerves and midbrain. A small pupil may be seen as part of the Horner syndrome—characterized by ipsilateral ptosis (droopy eyelid), miosis (constricted pupil), and anhidrosis (lack of sweating) of the face. Horner syndrome may be congenital or may be caused by a lesion of the sympathetic pathway in the hypothalamus, brainstem, cervical spinal cord, or sympathetic plexus. Localization of the lesion within the sympathetic nervous system may be obvious given the other signs present or may be uncertain. In the latter case, serial testing with cocaine drops followed by hydroxyamphetamine drops may be helpful.

During the examination of the pupil, any abnormalities of the iris should also be noted (e.g., heterochromia, Brushfield spots). The physician should also assess the posterior segment of the eye using the red reflex test, which is performed in a darkened room using a direct ophthalmoscope held close to the examiner's eye and 12-18 inches from the infant's eyes. If the posterior segment of the eye is normal, the examiner should see symmetric reddish-pink retinal reflections. The absence of any red reflex or the presence of a blunted reflex, white reflex (leukocoria), or red reflex with dark spots all signal pathology and should prompt referral to an ophthalmologist.
Oculomotor (Cranial Nerve III), Trochlear (Cranial Nerve IV), and Abducens Nerves (Cranial Nerve VI)

The globe is moved by 6 extraocular muscles, which are innervated by the oculomotor, trochlear, and abducens nerves. These muscles and nerves can be assessed by having the patient follow an interesting toy or the examiner’s finger in the 6 cardinal directions of gaze. The physician observes the range and nature (conjugate vs dysconjugate, smooth vs choppy or saccadic) of the eye movements, particularly noting the presence and direction of any abnormal eye movements. Premature infants older than 25 wk of gestational age and comatose patients can have slightly disconjugate gaze at rest, with 1 eye displaced from the other by 1 or 2 mm beyond the midline. Patients with increased ICP often respond positively when questioned about double vision (diplopia) and exhibit incomplete abduction of the eyes on lateral gaze as a result of partial VIth nerve palsies. This false-localizing sign occurs because CN VI has a long intracranial course, making it particularly susceptible to being stretched. Internuclear ophthalmoplegia, caused by a lesion in the medial longitudinal fasciculus of the brainstem, that functionally serves conjugate gaze by connecting CN VI on one side to CN III on the other, results in paralysis of medial rectus function in the adducting eye and nystagmus in the abducting eye.

When there is a subtle eye movement abnormality, the red glass test may be helpful in localizing the lesion. To perform this test, a red glass is placed over one of the patient’s eyes and the patient is instructed to follow a white light in all directions of gaze. The child sees 1 red/white light in the direction of normal muscle function but notes a separation of the red and white images that is greatest in the plane of action of the affected muscle.

In addition to gaze palsies, the examiner might encounter a variety of adventitious movements. Nystagmus is an involuntary, rapid movement of the eye that may be subclassified as being pendular, in which the 2 phases have equal amplitude and velocity, or jerk, in which there is a fast and slow phase. Jerk nystagmus can be further characterized by the direction of its fast phase, which may be left-, right-, up-, or downbeating; rotatory; or mixed. Many patients have a few beats of nystagmus with extreme lateral gaze (end-gaze nystagmus), which is
of no consequence. Pathologic horizontal nystagmus is most often congenital, drug-induced (e.g., alcohol, anticonvulsants), or a result of vestibular system dysfunction. By contrast, vertical nystagmus is often associated with structural abnormalities of the brainstem and cerebellum. Ocular bobbing is characterized by a downward jerk followed by a slow drift back to primary position and is associated with pontine lesions. Opsoclonus describes involuntary, chaotic oscillations of the eyes, which are often seen in the setting of neuroblastoma or viral infection.

**Trigeminal Nerve (Cranial Nerve V)**
The 3 divisions of the trigeminal nerve—ophthalmic, maxillary, and mandibular—convey information about facial protopathic (pain, temperature) and epicritic (vibration, proprioception) sensation. Each modality should be tested and compared to the contralateral side. In patients who are uncooperative or comatose, the integrity of the trigeminal nerve can be assessed by the corneal reflex, elicited by touching the cornea with a small pledget of cotton and observing for symmetric eye closure, and nasal tickle, obtained by stimulating the nasal passage with a cotton swab and observing for symmetric grimace. An absent reflex may be because of a sensory defect (trigeminal nerve) or a motor deficit (facial nerve). The motor division of the trigeminal nerve can be tested by examining the masseter, pterygoid, and temporalis muscles during mastication, as well as by evaluation of the jaw jerk.

**Facial Nerve (Cranial Nerve VII)**
The facial nerve is a predominantly motor nerve that innervates the muscles of facial expression, buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric. It also has a separate division, called the chorda tympani, that contains sensory, special sensory (taste), and parasympathetic fibers. Because the portion of the facial nucleus that innervates the upper face receives bilateral cortical input, lesions of the motor cortex or corticobulbar tract have little effect on upper face strength. Rather, such lesions manifest with flattening of the contralateral nasolabial fold or dropping of the corner of the mouth. Conversely, lower motor neuron or facial nerve lesions tend to involve upper and lower facial muscles equally. Facial strength can be evaluated by observing the patient's spontaneous movements and by asking the patient to mimic a series of facial movements (e.g., smiling, raising the eyebrows, inflating the cheeks). A facial nerve palsy may be congenital; idiopathic (Bell palsy); or secondary to trauma, demyelination (Guillain-Barré syndrome), infection (Lyme disease, herpes simplex virus, HIV), granulomatous disease, neoplasm, or meningeal inflammation or infiltration. Facial nerve lesions that are proximal to the junction with the chorda tympani will result in an inability to taste substances with the anterior two-thirds of the tongue. If necessary, taste can be tested by placing a solution of saline or glucose on 1 side of the extended tongue. Normal children can identify the test substance in <10 sec. Other findings that may be associated with facial nerve palsy include hyperacusis, resulting from stapedius muscle involvement, and impaired tearing.

**Vestibulocochlear Nerve (Cranial Nerve VIII)**
The vestibulocochlear nerve has 2 components within a single trunk: the vestibular nerve, which innervates the semicircular canals of the inner ear and is involved with equilibrium, coordination, and orientation in space, and the cochlear nerve, which innervates the cochlea and subserves hearing.

Dysfunction of the vestibular system results in vertigo, the sensation of environmental motion. On examination, patients with vestibular nerve dysfunction typically have nystagmus, in which the fast component is directed away from the affected nerve. With their arms outstretched and eyes closed, their limbs tend to drift toward the injured side. Likewise, if they march in place, they slowly pivot toward the lesion (Fukuda stepping test). On Romberg and tandem gait testing, they tend to fall toward the abnormal ear. Vestibular function can be further evaluated with caloric testing. Before testing, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. In an obtunded or comatose patient, 30-50 mL of ice water is then delivered by syringe into the external auditory canal with the patient's head elevated 30 degrees. If the brainstem is intact, the eyes deviate toward the irritated side. A much smaller quantity of ice water (2 mL) is used in awake, alert patients to avoid inducing nausea. In normal subjects, introduction of ice water produces eye deviation toward the stimulated labyrinth followed by nystagmus with the fast component away from the stimulated labyrinth.

Because hearing is integral to normal language development, the physician should inquire directly about hearing problems. Parents' concern is often a reliable indicator of hearing impairment and warrants a formal audiologic assessment with either audiometry or brainstem auditory evoked potential testing (see Chapter 637). Even in the absence of parents' concern, certain children warrant formal testing within the 1st mo of life, including those with a family history of early life or syndromic deafness or a personal history of prematurity, severe asphyxia, exposure to ototoxic drugs, hyperbilirubinemia, congenital anomalies of the head or neck, bacterial meningitis, and congenital TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections. For all other infants and children, a simple bedside assessment of hearing is usually sufficient. Newborns might have subtle responses to auditory stimuli, such as changes in breathing, cessation of movement, or opening of the eyes and/or mouth. If the same stimulus is presented repeatedly, normal neonates cease to respond, a phenomenon known as habituation. By 3-4 mo of age, infants begin to orient to the source of sound. Hearing-impaired toddlers are visually alert and appropriately responsive to physical stimuli but might have more frequent temper tantrums and abnormal speech and language development.

**Glossopharyngeal Nerve (Cranial Nerve IX)**
The glossopharyngeal nerve conveys motor fibers to the stylopharyngeus muscle; general sensory fibers from the posterior third of the tongue, pharynx, tonsil, internal surface of the tympanic membrane, and skin of the external ear; special sensory (taste) fibers from the posterior third of the tongue; parasympathetic fibers to the parotid gland; and general visceral sensory fibers from the carotid bodies. The nerve is tested by stimulating 1 side of the lateral oropharynx or soft palate with a tongue blade and observing for symmetric elevation of the palate (gag reflex). An isolated lesion of CN IX is rare, because it runs in close proximity to CN X. Potential causes of injury and/or dysfunction include birth trauma, ischemia, mass lesions, motor neuron disease, retropharyngeal abscess, and Guillain-Barré syndrome.

**Vagus Nerve (Cranial Nerve X)**
The vagus nerve has 10 terminal branches: meningeal, auricular, pharyngeal, carotid body, superior laryngeal, recurrent laryngeal, cardiac, pulmonary, esophageal, and gastrointestinal. The pharyngeal, superior laryngeal, and recurrent laryngeal branches contain motor fibers that innervate all of the muscles of the pharynx and larynx, with the exception of the stylopharyngeus (CN IX) and tensor veli palatini (CN V) muscles. Thus, unilateral injury of the vagus nerve results in weakness of the ipsilateral soft palate and a hoarse voice; bilateral lesions can produce respiratory distress as a result of vocal cord paralysis, as well as nasal regurgitation of fluids, pooling of secretions, and an immobile, low-lying soft palate. Isolated lesions to the vagus nerve may be a complication of thoracotomies or may be seen in neonates with type II Chiari malformations. If such a lesion is suspected, it is important to visualize the vocal cords. In addition to motor information, the vagus nerve carries somatic afferents from the pharynx, larynx, ear canal, external surface of the tympanic membrane, and meninges of the posterior fossa; visceral afferents; taste fibers from the posterior pharynx; and preganglionic parasympathetics.

**Accessory Nerve (Cranial Nerve XI)**
The accessory nerve innervates the sternocleidomastoid (SCM) and trapezius muscles. The left SCM acts to turn the head to the right side and vice versa; acting together, the SCMs flex the neck. The trapezius
acts to elevate the shoulder. Lesions to the accessory nerve result in atrophy and paralysis of the ipsilateral SCM and trapezius muscles, with resultant depression of the shoulder. Because several cervical muscles are involved in head rotation, unilateral SCM paresis might not be evident unless the patient is asked to rotate the head against resistance. Skull base fractures or lesions, motor neuron disease, myotonic dystrophy, and myasthenia gravis commonly produce atrophy and weakness of these muscles; congenital torticollis is associated with SCM hypertrophy.

**Hypoglossal Nerve (Cranial Nerve XII)**

The hypoglossal nerve innervates the tongue. Examination of the tongue includes assessment of its bulk and strength, as well as observation for adventitious movements. Malfunction of the hypoglossal nucleus or nerve produces atrophy, weakness, and fasciculations of the tongue. If the injury is unilateral, the tongue deviates toward the side of the injury; if it is bilateral, tongue protrusion is not possible and the patient can have difficulty swallowing (dysphagia). Werdnig-Hoffmann disease (infantile spinal muscular atrophy, or spinal muscular atrophy type 1) and congenital anomalies in the region of the foramen magnum are the principal causes of hypoglossal nerve dysfunction.

**Motor Examination**

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for involuntary movements that might indicate central or peripheral nervous system pathology.

**Bulk**

Decreased muscle bulk (atrophy) may be secondary to disuse or to diseases of the lower motor neuron, nerve root, peripheral nerve, or muscle. In most cases, neurogenic atrophy is more severe than myogenic atrophy. Increased muscle bulk (hypertrophy) is usually physiologic (e.g., body builders). Pseudohypertrophy refers to muscle tissue that has been replaced by fat and connective tissue, giving it a bulky appearance with a paradoxical reduction in strength, as in Duchenne muscular dystrophy.

**Tone**

Muscle tone, which is generated by an unconscious, continuous, partial contraction of muscle, creates resistance to passive movement of a joint. Tone varies greatly based on a patient’s age and state. At 28 wk of gestation, all 4 extremities are extended and there is little resistance to passive movement. Flexor tone is visible in the lower extremities at 32 wk and is palpable in the upper extremities at 36 wk; a normal-term infant’s posture is characterized by flexion of all 4 extremities.

There are 3 key tests for assessing postural tone in neonates: the traction response, vertical suspension, and horizontal suspension (Fig. 590-3; see Chapters 94 and 97). To evaluate the traction response, the physician grasps the infant’s hands and gently pulls the infant to a sitting position. Normally, the infant’s head lags slightly behind the infant’s body and then falls forward upon reaching the sitting position. To test vertical suspension, the physician holds the infant by the axillae without gripping the thorax. The infant should remain suspended with the infant’s lower extremities held in flexion; a hypotonic infant will slip through the physician’s hands. With horizontal suspension, the physician holds the infant prone by placing a hand under the infant’s abdomen. The head should rise and the limbs should flex, but a hypotonic infant will drape over the physician’s hand, forming a U shape. Assessing tone in the extremities is accomplished by observing the infant’s resting position and passively manipulating the infant’s limbs. When the upper extremity of a normal-term infant is pulled gently across the chest, the elbow does not quite reach the mid-sternum (scarf sign), whereas the elbow of a hypotonic infant extends beyond the midline with ease. Measurement of the popliteal angle is a useful method for documenting tone in the lower extremities. The examiner flexes the hip and extends the knee. Normal-term infants allow
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Floppy and often assumes a frog-leg posture at rest. Hypotonia can reflect pathology of the cerebral hemispheres, cerebellum, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.

**Strength**

Older children are usually able to cooperate with formal strength testing, in which case muscle power is graded on a scale of 0-5 as follows: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; 5 = normal power. An examination of muscle power should include all muscle groups, including the neck flexors and extensors and the muscles of respiration. It is important not only to assess individual muscle groups, but also to determine the pattern of weakness (i.e., proximal vs distal; segmental vs regional). Testing for pronator drift can be helpful in localizing the lesion in a patient with weakness. This test is accomplished by having the patient extend his or her arms away from the body with the palms facing upward and the eyes closed. Together, pronation and downward drift of an arm indicate a lesion of the contralateral corticospinal tract.

Because infants and young children are not able to participate in formal strength testing, they are best assessed with functional measures. Proximal and distal strength of the upper extremities can be tested by having the child reach overhead for a toy and by watching the child manipulate small objects. In infants younger than 2 mo old, the physician can also take advantage of the palmar grasp reflex in assessing distal power and the Moro reflex in assessing proximal power. Infants with decreased strength in the lower extremities tend to have diminished spontaneous activity in their legs and are unable to support their body weight when held upright. Older children may have difficulty climbing or descending steps, jumping, or hopping. They might also use their hands to “climb up” their legs when asked to rise from a prone position, a maneuver called Gowers sign (Fig. 590-5).

**Involuntary Movements**

Patients with lower motor neuron or peripheral nervous system lesions might have fasciculations, which are small, involuntary muscle contractions that result from the spontaneous discharge of a single motor unit and create the illusion of a “bag of worms” under the skin. Because most infants have abundant body fat, muscle fasciculations are best observed in the tongue in this age group.

Most other involuntary movements, including tics, dystonia, chorea, and athetosis, stem from disorders of the basal ganglia. Tremor seems...
Table 590-2  Timing of Selected Primitive Reflexes

<table>
<thead>
<tr>
<th>REFLEX</th>
<th>ONSET</th>
<th>FULLY DEVELOPED</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar grasp</td>
<td>28 wk gestation</td>
<td>32 wk gestation</td>
<td>2-3 mo postnatal</td>
</tr>
<tr>
<td>Rooting</td>
<td>32 wk gestation</td>
<td>36 wk gestation</td>
<td>Less prominent after 1 mo postnatal</td>
</tr>
<tr>
<td>Moro</td>
<td>28-32 wk gestation</td>
<td>37 wk gestation</td>
<td>5-6 mo postnatal</td>
</tr>
<tr>
<td>Tonic neck</td>
<td>35 wk gestation</td>
<td>1 mo postnatal</td>
<td>6-7 mo postnatal</td>
</tr>
<tr>
<td>Parachute</td>
<td>7-8 mo postnatal</td>
<td>10-11 mo postnatal</td>
<td>Remains throughout life</td>
</tr>
</tbody>
</table>

to be an exception, as it is thought to be mediated by cerebellomacular pathways. Further detail on the individual movement disorders is provided in Chapter 597.

Sensory Examination
The sensory examination is difficult to perform on an infant or uncooperative child and has a relatively low yield in terms of the information that it provides. A gross assessment of sensory function can be achieved by distracting the patient with an interesting toy and then touching the patient with a cotton swab in different locations. Normal infants and children indicate an awareness of the stimulus by crying, withdrawing the extremity, or pausing briefly; however, with repeated testing, they lose interest in the stimulus and begin to ignore the examiner. It is critical, therefore, that any areas of concern are tested efficiently and, if necessary, reexamined at an appropriate time.

Fortunately, isolated disorders of the sensory system are less common in the very young pediatric population than in the adult population, so detailed sensory testing is rarely warranted. Furthermore, most patients who are old enough to voice a sensory complaint are also old enough to cooperate with formal testing of light touch, pain, temperature, vibration, proprioception, and corticosenso...
testing forces patients to have a narrow base, which highlights subtle balance difficulties.

There are a variety of abnormal gaits, many of which are associated with a specific underlying etiology. Patients with a spastic gait appear stiff-legged like a soldier. They may walk on tiptoe as a result of tightness or contractures of the Achilles tendons, and their legs may scissors as they walk. A hemiparetic gait is associated with spasticity and circumduction of the leg, as well as decreased arm swing on the affected side. Cerebellar ataxia results in a wide-based, reeling gait like a drunk person, whereas sensori motor ataxia results in a wide-based step gait, in which the patient lifts the legs up higher than usual in the swing phase and then slaps the foot down. A myopathic, or waddling, gait is associated with hip girdle weakness. Affected children often develop a compensatory lordosis and have other signs of proximal muscle weakness, such as difficulty climbing stairs. During gait testing, the examiner may also note hypotonia or weakness of the lower extremities; extrapyramidal movements, such as dystonia or chorea; or orthopedic deformities, such as pelvic tilt, genu recurvatum, varus or valgus deformities of the knee, pes cavus (high arches) or pes planus (flat feet), and scoliosis.

GENERAL EXAMINATION
Examination of other organ systems is essential because myriad systemic diseases affect the nervous system. Dystrophic features can indicate a genetic syndrome (see Chapter 108). Heart murmurs may be associated with rheumatic fever (Sydenham chorea), cardiac rhabdomyoma (tuberous sclerosis), cyanotic heart disease (cerebral abscess or thrombosis), and endocarditis (cerebral vascular occlusion). Hepatosplenomegaly can suggest an inborn error of metabolism, storage disease, HIV, or malnutrition. Cutaneous lesions may be a feature of a neurocutaneous syndrome (see Chapter 596).

SPECIAL DIAGNOSTIC PROCEDURES
Lumbar Puncture and Cerebrospinal Fluid Examination
Examination of the cerebrospinal fluid (CSF) and measurement of the pressure it creates in the subarachnoid space are essential in confirming the diagnosis of meningitis, encephalitis, and idiopathic intracranial hypertension (previously referred to as pseudotumor cerebri), and it is often helpful in assessing subarachnoid hemorrhage; demyelinating, degenerative, and collagen vascular diseases; and intracranial neoplasms. Having an experienced assistant who can position, restrain, and comfort the patient is critical to the success of the procedure.

The patient should be situated in a lateral decubitus or seated position with the neck and legs flexed to enlarge the intervertebral spaces. As a rule, sick neonates should be maintained in a seated position to prevent problems with ventilation and perfusion. Regardless of the position chosen, it is important to make sure that the patient's shoulders and hips are straight to prevent rotating the spine.

Once the patient is situated, the physician identifies the appropriate interspace by drawing an imaginary line from the iliac crest downward perpendicular to the vertebral column. In adults, lumbar punctures are usually performed in the L3-L4 or L4-L5 interspaces. Next, the physician dons a mask, gown, and sterile gloves. The skin is thoroughly prepared with a cleansing agent, and sterile drapes are applied. The skin and underlying tissues are anesthetized by injecting a local anesthetic (e.g., 1% lidocaine) at the time of the procedure or by applying aeutectic mixture of lidocaine and prilocaine (EMLA) to the skin 30 minutes before the procedure. A 22-gauge, 1.5-3.0 in, sharp, beveled spinal needle with a properly fitting stylet is introduced in the midsagittal plane and directed slightly cephalad. The physician should pause frequently, remove the stylet, and assess for CSF flow. Although a pop can occur as the needle penetrates the dura, it is more common to experience a subtle change in resistance.

Once CSF has been detected, a manometer and 3-way stopcock can be attached to the spinal needle to obtain an opening pressure. If the patient was seated as the spinal needle was introduced, the patient should be moved carefully to a lateral decubitus position with the head and legs extended before the manometer is attached. Normal opening pressures are 90-120 mm H2O in newborns, 60-180 mm H2O in young children, and 12-120 mm H2O in older children and adults. The 90th percentile in children has been reported to be 250 mm of H2O. The most common cause of an elevated opening pressure is an agitated patient. Sedation and high body mass index can also increase the opening pressure.

Contraindications to performing a lumbar puncture include suspected mass lesion of the brain, especially in the posterior fossa or above the tentorium and causing shift of the midline; suspected mass lesion of the spinal cord; symptoms and signs of impending cerebral herniation in a child with probable meningitis; critical illness (on rare occasions); skin infection at the site of the lumbar puncture; and thrombocytopenia with a platelet count <20 x 10^9/L. If disc edema or focal findings suggest a mass lesion, a head CT should be obtained before proceeding with lumbar puncture to prevent uncal or cerebellar herniation as the CSF is removed. In the absence of these findings, routine head imaging is not warranted. The physician should also be alert to clinical signs of impending herniation, including alterations in the respiratory pattern (e.g., hyperventilation; Cheyne-Stokes respirations, ataxic respirations, respiratory arrest), abnormalities of pupil size and reactivity, loss of brainstem reflexes, and decorticate or decerebrate posturing. If any of these signs are present or the child is so ill that the lumbar puncture might induce cardiorespiratory arrest, blood cultures should be drawn and supportive care, including antibiotics, should be initiated. Once the patient has stabilized, it may be possible to perform a lumbar puncture safely.

Normal CSF contains no red blood cells; thus, their presence indicates a traumatic tap or a subarachnoid hemorrhage. Progressive clearing of the blood between the first and last samples indicates a traumatic tap. Bloody CSF should be centrifuged immediately. A clear supernatant is consistent with a bloody tap, whereas xanthochromia (yellow color that results from the degradation of hemoglobin) suggests a subarachnoid hemorrhage. Xanthochromia may be absent in bleeds <12 hr old, particularly when laboratories rely on visual inspection rather than spectroscopy. Xanthochromia can also occur in the setting of hyperbilirubinemia, carotenemia, and markedly elevated CSF protein.

The normal CSF protein is 10-40 mg/dL in a child and as high as 120 mg/dL in a neonate. The CSF protein falls to the normal childhood range by 3 mo of age. The CSF protein may be elevated in many processes, including infectious, immunologic, vascular, and degenerative diseases; blockage of CSF flow, as well as tumors of the brain (primary CNS tumors, systemic tumors metastatic to the CNS, infiltrative acute lymphoblastic leukemia) and spinal cord. With a traumatic tap, the CSF protein is increased by approximately 1 mg/dL for every 1,000 red blood cells/mm^3. Elevation of CSF immunoglobulin G, which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis, in postinfectious encephalomyelitis, and in some cases of multiple sclerosis. If the diagnosis of multiple sclerosis is suspected, the CSF should be tested for the presence of oligoclonal bands.

The CSF glucose content is approximately 60% of the blood glucose in a healthy child. To prevent a spuriously elevated blood:CSF glucose ratio in a case of suspected meningitis, it is advisable to collect the blood glucose before the lumbar puncture when the child is relatively calm. Hypoglycemia is found in association with diffuse meningeval disease, particularly bacterial and tuberculous meningitis. Wide spread neoplastic involvement of the meninges, subarachnoid hemorrhage, disorders involving the glucose transporter protein type 1, fungal meningitis, and, occasionally, aseptic meningitis can produce low CSF glucose as well.
A Gram stain of the CSF is essential if there is a suspicion for bacteriologic meningitis; an acid-fast stain and India ink preparation can be used to assess for tuberculous and fungal meningitis, respectively. CSF is then plated on different culture media depending on the suspected pathogen. When indicated by the clinical presentation, it can also be helpful to assess for the presence of specific antigens (e.g., latex agglutination for Neisseria meningitidis, Haemophilus influenzae type b, or Streptococcus pneumoniae) or to obtain antibody or polymerase chain reaction studies (e.g., herpes simplex virus-1 and -2, West Nile virus, enteroviruses). In noninfectious cases, levels of CSF metabolites, such as lactate, amino acids, and enolase, can provide clues to the underlying metabolic disease.

Neuroradiologic Procedures

Skull roentgenograms have limited diagnostic utility. They can demonstrate fractures, bony defects, intracranial calcifications, or indirect evidence of increased ICP. Acutely increased ICP causes separation of the sutures, whereas chronically increased ICP is associated with erosion of the posterior clinoïd processes, enlargement of the sella turcica, and increased convoluted markings.

Craniul ultrasonography is the imaging method of choice for detecting intracranial hemorrhage, periventricular leukomalacia, and hydrocephalus in infants with patent anterior fontanelles. Ultrasound is less sensitive than either CT or MRI for detecting hypoxic–ischemic injury, but the use of color Doppler or power Doppler sonography, both of which show changes in regional cerebral blood flow, improve its sensitivity. In general, ultrasonography is not a useful technique in older children, although it can be helpful intraoperatively when placing shunts, locating small tumors, and performing needle biopsies.

CT is a valuable diagnostic tool in the evaluation of many neurologic emergencies, as well as some nonemergent conditions. It is a noninvasive, rapid procedure that can usually be performed without sedation. CT scans use conventional x-ray techniques, meaning that they produce ionizing radiation. Because children younger than 10 yr of age are several times more sensitive to radiation than adults, it is important to consider the whether imaging is actually indicated and, if it is, whether an ultrasound or MRI might be the more appropriate study. In the emergency setting, a noncontrast CT scan can demonstrate skull fractures, pterional hemorrhages, hydrocephalus, and impending herniation. If the noncontrast scan reveals an abnormality and an MRI cannot be performed in a timely fashion, nonionic contrast should be used to highlight areas of breakdown in the blood–brain barrier (e.g., abscesses, tumors) and/or collections of abnormal blood vessels (e.g., arteriovenous malformations). CT is less useful for diagnosing acute infarcts in children, because radiographic changes might not be apparent for up to 24 hr. Some subtle signs of early (<24 hr) infarction include sulcal effacement, blurring of the gray–white junction, and the hyperdense middle cerebral artery sign (increased attenuation in the middle cerebral artery that is often associated with thrombosis). In the routine setting, CT imaging can be used to demonstrate intracranial calcifications or, with the addition of 3-dimensional reformating, to evaluate patients with craniofacial abnormalities or craniosynostosis. Although other pathologic processes may be visible on CT scan, MR is generally preferred because it provides a more-detailed view of the anatomy without exposure to ionizing radiation (Table 590-3).

CT angiography is a useful tool for visualizing vascular structures and is accomplished by administering a tight bolus of iodinated contrast through a large-bore intravenous catheter and then acquiring CT images as the contrast passes through the arteries.

MRI is a noninvasive procedure that is well suited for detecting a variety of abnormalities, including those of the posterior fossa and spinal cord. MRI scans are highly susceptible to patient motion artifact; consequently, many children younger than age 8 yr require sedation to ensure an adequate study. (The need for sedation is beginning to change in some centers as MRI technology improves and allows for faster performance of studies.) Because the American Academy of Pediatrics recommends that infants be kept nothing by mouth (NPO) for 4 hr or longer and older children for 6 hr or longer before deep sedation, it is often difficult to obtain an MRI on an infant or young child in the acute setting. MRI can be used to evaluate for congenital or acquired brain lesions, migrational defects, dysmyelination or demyelination, posttraumatic glisis, neoplasms, cerebral edema, and acute stroke (see Table 590-3). Paramagnetic MR contrast agents (e.g., gadolinium-dihydroxyethylenediaminepentaacetic acid [DTPA]) are efficacious in identifying areas of disruption in the blood–brain barrier, such as those occurring in primary and metastatic brain tumors, meningitis, cerebritis, abscesses, and active demyelination. MR angiography and MR venography provide detailed images of major intracranial vascular structures and assist in the diagnosis of conditions such as stroke, vascular malformations, and cerebral venous sinus thrombosis. MR angiography is the procedure of choice for infants and young children owing to the lack of ionizing radiation and contrast; however, CT angiography may be preferable in older children because it is faster and can eliminate the need for sedation; it is particularly useful for looking at blood vessels in the neck, where there is less interference from bone artifact than in the skull-encased brain.

Functional MRI is a noninvasive technique used to map neural activity during specific cognitive states and/or sensorimotor functions. Data are usually based on blood oxygenation, although they can also be based on local cerebral blood volume or flow. Functional MRI is useful for presurgical localization of critical brain functions and has several advantages over other functional imaging techniques. Specifically, functional MRI produces high-resolution images without exposure to ionizing radiation or contrast, and it allows coregistration of functional and structural images.

Proton MR spectroscopy (MRS) is a molecular imaging technique in which the unique neurochemical profile of a preselected brain region is displayed in the form of a spectrum. Many metabolites can be detected, the most common of which are N-acetylaspartate, creatine and phosphocreatine, choline, myoinositol, and lactate. Changes in the spectral pattern of a given area can yield clues to the underlying pathology, making MRS useful in the diagnosis of inborn errors of metabolism, as well as the preoperative and posttherapeutic assessment of intracranial tumors. MRS can also detect areas of cortical dysplasia in patients with epilepsy, because these patients have low N-acetylaspartate:creatine ratios. Finally, MRS may be useful in detecting hypoxic–ischemic injury in newborns in the 1st day of life, because the lactate peak enlarges and the N-acetylaspartate peak diminishes before MRI sequences become abnormal.

Catheter angiography is the gold standard for diagnosing vascular disorders of the CNS, such as arteriovenous malformations, aneurysms, arterial occlusions, and vasculitis. A 4-vessel study is accomplished by introducing a catheter into the femoral artery and then injecting contrast media into each of the internal carotid and vertebral arteries. Because catheter angiography is invasive and requires general anesthesia, it is typically reserved for treatment planning of endovascular or open procedures and for cases in which noninvasive imaging results are not diagnostic.

Positron emission tomography provides unique information on brain metabolism and perfusion by measuring blood flow, oxygen uptake, and/or glucose consumption. Positron emission tomography is an expensive technique that is gaining a following in some pediatric centers, particularly those with active epilepsy surgery programs.

Single-photon emission CT using 99mTc hexamethylpropyleneamine oxime is a sensitive and inexpensive technique to study regional cerebral blood flow. Single-photon emission CT is particularly useful in assessing for vasculitis, herpes encephalitis, dysplastic cortex, and recurrent brain tumors. Positron emission tomography MRI is only available in a few pediatric centers in the United States; it provides better resolution and tissue definition than single-photon emission CT.

Electroencephalography

An electroencephalogram (EEG) provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it likely originates from postsynaptic potentials in the dendrites of cortical neurons. Even with amplification of the electrical activity, not all potentials are recorded because there is a buffering effect of the scalp, muscles, bone, vessels, and subarachnoid fluid. EEG waves are...
Table 590-3 Preferred Imaging Procedures in Neurologic Diseases

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Imaging Procedures</th>
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<tbody>
<tr>
<td><strong>ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK</strong></td>
<td>CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions. Otherwise, MRI/MRA (head and neck) with and without gadolinium and diffusion-weighted images. If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA. Obtain an MRV if the infarct does not follow an arterial distribution. CT or MRI can detect infarcts more than 24 hr old, although MRI is generally preferred to avoid exposure to ionizing radiation.</td>
</tr>
<tr>
<td><strong>INTRAPARENCHYMAL HEMORRHAGE</strong></td>
<td>CT if &lt;24 hr; MRI if &gt;24 hr. MRI and MRA to assess for underlying vascular malformation, tumor, etc. Catheter angiography if MRA is nondiagnostic.</td>
</tr>
<tr>
<td><strong>ARTERIOVENOUS MALFORMATION</strong></td>
<td>CT for acute hemorrhage, MRI and MRA with and without gadolinium as early as possible. Catheter angiography if noninvasive imaging is nondiagnostic.</td>
</tr>
<tr>
<td><strong>CEREBRAL ANEURYSM</strong></td>
<td>CT without contrast for acute subarachnoid hemorrhage. MRI or CTA to identify the aneurysm. Catheter angiography may be necessary in some cases. TCD to detect vasospasm.</td>
</tr>
<tr>
<td><strong>HYPOXIC-ISCHEMIC BRAIN INJURY</strong></td>
<td>Ultrasound in infants. If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI. In older children, CT if unstable; otherwise, MRI. MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes.</td>
</tr>
<tr>
<td><strong>METABOLIC DISORDERS</strong></td>
<td>MRI, particularly T2-weighted and FLAIR images. Diffusion-weighted images may be useful in distinguishing acute and chronic changes. MRS, SPECT, and PET may be useful in certain disorders.</td>
</tr>
<tr>
<td><strong>HYDROCEPHALUS</strong></td>
<td>Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus. MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus. Ultrasound (in infants) or CT to follow ventricular size in response to treatment.</td>
</tr>
<tr>
<td><strong>HEADACHE</strong></td>
<td>CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations as it does not involve ionizing radiation and provides a better view of the parenchyma).</td>
</tr>
<tr>
<td><strong>HEAD TRAUMA</strong></td>
<td>CT without contrast initially. MRI after initial assessment and treatment if clinically indicated. Diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities.</td>
</tr>
<tr>
<td><strong>EPILEPSY</strong></td>
<td>MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected. PET, interictal SPECT.</td>
</tr>
<tr>
<td><strong>BRAIN TUMOR</strong></td>
<td>MRI with and without gadolinium. Obtain sagittal FLAIR images.</td>
</tr>
<tr>
<td><strong>MULTIPLE SCLEROSIS</strong></td>
<td>CT without contrast and with contrast if there are signs of increased ICP on examination. MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis.</td>
</tr>
<tr>
<td><strong>BRAIN ABSCESS</strong></td>
<td>MRI with and without gadolinium. Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor. If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible.</td>
</tr>
<tr>
<td><strong>MOVEMENT DISORDERS</strong></td>
<td>MRI with and without gadolinium. PET. DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes).</td>
</tr>
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</table>

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

classified according to their frequency as delta (1-3/sec), theta (4-7/sec), alpha (8-12/sec), and beta (13-20/sec). These waves are altered by many factors, including age, level of alertness, eye closure, drugs, and disease states.

The normal waking EEG is characterized by the posterior dominant rhythm—a sinusoidal, 8-12 Hz rhythm that is most prominent over the occipital region in a state of relaxed wakefulness with the eyes closed. This rhythm first becomes apparent at 3-4 mo old, and most children have achieved the adult frequency of 8-12 Hz by age 8 yr.

Normal sleep is divided into 3 stages of non–rapid eye movement sleep—designated N1, N2, and N3—and rapid eye movement sleep. N1 corresponds to drowsiness, and N3 represents deep, restorative, slow-wave sleep. Rapid eye movement sleep is rarely captured during a routine EEG but may be seen on an overnight recording. The American Electroencephalography Society Guideline and Technical Standards states that “sleep recordings should be obtained whenever possible”; however, it appears that sleep deprivation—not sleep during the EEG—is what increases the yield of the study, particularly in children with 1 or more clinically diagnosed seizures and in children older than 3 yr of age.

EEG abnormalities can be divided into 2 general categories: epileptiform discharges and slowing. Epileptiform discharges are paroxysmal spikes or sharp waves, often followed by slow waves, which interrupt the background activity. They may be focal, multifocal, or generalized. Focal discharges are often associated with cerebral dysgenesis or irritative lesions, such as cysts, slow-growing tumors, or glial scar tissue; generalized discharges typically occur in children with structurally normal brains. Generalized discharges can occur as an epilepsy trait in children who have never had a seizure and, by themselves, are not an indication for treatment. Epileptiform activity may be enhanced by activation procedures, including hyperventilation and photic stimulation.

As with epileptiform discharges, slowing can be either focal or diffuse. Focal slowing should raise a concern for an underlying functional or structural abnormality, such as an infarct, hematoma, or tumor. Diffuse slowing is the hallmark of encephalopathy and is usually secondary to a widespread disease process or toxic–metabolic insult.

Long-term video EEG monitoring provides precise characterization of seizure types, which allows specific medical or surgical management. It facilitates more accurate differentiation of epileptic seizures.
from paroxysmal events that mimic epilepsy, including psychogenic nonepileptiform attacks. Long-term EEG monitoring can also be useful during medication adjustments.

**Evoked Potentials**

An evoked potential is an electrical signal recorded from the CNS following the presentation of a specific visual, auditory, or sensory stimulus. Stimulation of the visual system by a flash or patterned stimulus, such as a black-and-white checkerboard, produces visual evoked potentials (VEPs), which are recorded over the occiput and averaged in a computer. Abnormal VEPs can result from lesions to the visual pathway anywhere from the retina to the visual cortex. Many demyelinating disorders and neurodegenerative diseases, such as Tay-Sachs, Krabbe, or Pelizaeus-Merzbacher disease, or neuronal ceroid lipofuscinoses, show characteristic VEP abnormalities. Flash VEPs can also be helpful in evaluating infants who have sustained an anoxic injury; however, detection of an evoked potential does not necessarily mean that the infant will have functional vision.

**Brainstem auditory evoked responses (BAERs)** provide an objective measure of hearing and are particularly useful in neonates and in children who have failed, or are uncooperative with, audiometric testing. BAERs are abnormal in many neurodegenerative diseases of childhood and are an important tool in evaluating patients with suspected tumors of the cerebellopontine angle. BAERs can be helpful in assessing brainstem function in comatose patients, because the waveforms are unaffected by drugs or by the level of consciousness; however, they are not accurate in predicting neurologic recovery and outcome.

**Somatosensory evoked potentials (SSEPs)** are obtained by stimulating a peripheral nerve (peroneal, median) and then recording the electrical response over the cervical region and contralateral parietal somatosensory cortex. SSEPs determine the functional integrity of the dorsal column–medial lemniscal system and are useful in monitoring spinal cord function during operative procedures for scoliosis, aortic coarctation, and myelomeningocele repair. SSEPs are abnormal in many neurodegenerative disorders and are the most accurate evoked potential in the assessment of neurologic outcome following a severe CNS insult.

*Bibliography is available at Expert Consult.*
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Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close spontaneously between the 3rd and 4th wk of in utero development. Although the precise cause of NTDs remains unknown, evidence suggests that many factors, including hyperthermia, drugs (valproic acid), malnutrition, low red cell folate levels, chemicals, maternal obesity or diabetes, and genetic determinants (mutations in folate-responsive or folate-dependent enzyme pathways) can adversely affect normal development of the CNS from the time of conception. In some cases, an abnormal maternal nutritional state or exposure to radiation before conception increases the likelihood of a congenital CNS malformation. The major NTDs include spina bifida occulta, meningocele, myelomeningocele, encephalocele, anencephaly, caudal regression syndrome, dermal sinus, tethered cord, syringomyelia, diastematomyelia, and lipoma involving the conus medullaris and/or filum terminale and the rare condition iniencephaly.

The human nervous system originates from the primitive ectoderm that also develops into the epidermis. The ectoderm, endoderm, and mesoderm form the three primary germ layers that are developed by the 3rd wk. The endoderm, particularly the notochordal plate and the intraembryonic mesoderm, induces the overlying ectoderm to develop the neural plate in the 3rd wk of development (Fig. 591-1A). Failure of normal induction is responsible for most of the NTDs, as well as disorders of prosencephalic development. Rapid growth of cells within the neural plate causes further invagination of the neural groove and differentiation of a conglomerate of cells, the neural crest, which migrate laterally on the surface of the neural tube (Fig. 591-1B). The notochordal plate becomes the centrally placed notochord, which acts as a foundation around which the vertebral column ultimately develops. With formation of the vertebral column, the notochord undergoes involution and becomes the nucleus pulposus of the intervertebral disks. The neural crest cells differentiate to form the peripheral nervous system, including the spinal and autonomic ganglia and the ganglia of cranial nerves V, VII, VIII, IX, and X. In addition, the neural crest forms the leptomeninges, as well as Schwann cells, which are responsible for myelination of the peripheral nervous system. The dura is thought to arise from the paraxial mesoderm. In the region of the embryo destined to become the head, similar patterns exist. In this region, the notochord is replaced by the prechordal mesoderm.

In the 3rd wk of embryonic development, invagination of the neural groove is completed and the neural tube is formed by separation from the overlying surface ectoderm (see Fig. 591-1C). Initial closure of the neural tube is accomplished in the area corresponding to the future junction of the spinal cord and medulla and moves rapidly both caudally and rostrally. For a brief period, the neural tube is open at both ends, and the neural canal communicates freely with the amniotic cavity (see Fig. 591-1D). Failure of closure of the neural tube allows excretion of fetal substances (α-fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid, serving as biochemical markers for a NTD. Prenatal screening of maternal serum for AFP in the 16th-18th wk of gestation is an effective method for identifying pregnancies at risk for fetuses with NTDs in utero. Normally, the rostral end of the neural

Central nervous system (CNS) malformations are grouped into neural tube defects and associated spinal cord malformations; encephaloceles; disorders of structure specification (gray matter structures, neuronal migration disorders, disorders of connectivity, and commissure and tract formation); disorders of the posterior fossa, brainstem, and cerebellum; disorders of brain growth and size; and disorders of skull growth and shape. Classification of these conditions into syndromic, nonsyndromic, and single-gene etiologies is also important. These disorders can also be seen as isolated findings or as being a consequence of environmental exposures. Elucidation of single-gene causes has out-
Bibliography


Spina bifida occulta is a common anomaly consisting of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges. Most patients are asymptomatic and lack neurologic signs, and the condition is usually of no consequence. Some consider the term spina bifida occulta to denote merely a posterior vertebral body fusion defect. This simple defect does not have an associated spinal cord malformation. Other clinically more significant forms of this closed spinal cord malformation are more correctly termed occult spinal dysraphism. In most of these cases, there are cutaneous manifestations such as a hemangioma, discoloration of the skin, pit, lump, dermal sinus, or hairy patch (Fig. 591-2). A spine roentgenogram in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1; there is no abnormality of the meninges, spinal cord, or nerve roots. Occult spinal dysraphism is often associated with more significant developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, lipoma, fatty filum, dermal sinus, and/or a tethered cord. A spine x-ray in these cases might show bone defects or may be normal. All cases of occult spinal dysraphism are best investigated with MRI (Fig. 591-3). Initial screening in the neonate may include ultrasonography, but MRI is more accurate at any age.

A dermoid sinus usually forms a small skin opening, which leads into a narrow duct, sometimes indicated by protruding hairs, a hairy patch, or a vascular nevus. Dermoid sinuses occur in the midline at the sites where meningoceles or encephaloceles can occur: the lumbosacral region or occiput, respectively and occasionally in the cervical or thoracic area. Dermoid sinus tracts can pass through the dura, acting as a conduit for the spread of infection. Recurrent meningitis of occult origin should prompt careful examination for a small sinus tract in the posterior midline region, including the back of the head. Lower back sinuses are usually above the gluteal fold and are directed cephalad. Tethered spinal cord syndrome may also be an associated problem. Diastematomyelia commonly has bony abnormalities that require surgical intervention along with untethering of the spinal cord.

An approach to imaging of the spine in patients with cutaneous lesions is noted in Table 591-1.

Figure 591-3 Clinical features and imaging findings associated with occult spinal dysraphism. A, Lumbosacral lipoma. The subcutaneous lipoma is in continuity with the spinal cord via a defect in the underlying muscles bone and dura. B, Sagittal T1-weighted image shows huge intradural lipoma, merging with the conus medullaris superiorly. C, Lipoma and central dermal sinus. D and E, Dermal sinus with dermoid on an 8 yr old girl. Slightly parasagittal T2-weighted image shows sacral dermal sinus coursing obliquely downward in subcutaneous fat (arrow) (D). Midsagittal T2-weighted image shows huge dermoid in the thecal sac (arrowheads), extending upward to the tip of the conus medullaris (E). The mass gives a slightly lower signal than cerebrospinal fluid and is outlined by a thin low-signal rim. (A from Thompson DNP: Spinal dysraphic anomalies: classification, presentation and management. Paed Child Health 24:431–438, 2014, Fig. 4; B, D, and E from Rossi A, Biancheri R, Cama A, et al: Imaging in spine and spinal cord malformations, Eur J Radiol 50(2):177–200, 2004, Fig. 9a; and C, from Jaiswal AK, Garg A, Mahapatra AK: Spinal ossifying lipoma, J Clin Neurosci 12:714–717, 2005, Fig. 1.)
591.3 Meningocele  
Stephen L. Kinsman and Michael V. Johnston

A meningocele is formed when the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum. The spinal cord is usually normal and assumes a normal position in the spinal canal, although there may be tethering of the cord, syringomyelia, or diastematomyelia. A fluctuant midline mass that might transilluminate occurs along the vertebral column, usually in the lower back. Most meningoceles are well covered with skin and pose no immediate threat to the patient. Careful neurologic examination is mandatory. Orthopedic and urologic examination should also be considered. In asymptomatic children with normal neurologic findings and full-thickness skin covering the meningocele, surgery may be delayed or sometimes not performed.

Before surgical correction of the defect, the patient must be thoroughly examined with the use of plain x-rays, ultrasonography, and MRI to determine the extent of neural tissue involvement, if any, and associated anomalies, including diastematomyelia, lipoma, and possible clinically significant tethered spinal cord. Urologic evaluation usually includes cystometrogram to identify children with neurogenic bladder who are at risk for renal deterioration. Patients with leaking cerebrospinal fluid (CSF) or a thin skin covering should undergo immediate surgical treatment to prevent meningitis. A CT scan or MRI of the head is recommended for children with a meningocele because of the association with hydrocephalus in some cases. An anterior meningocele projects into the pelvis through a defect in the sacrum. Symptoms of constipation and bladder dysfunction develop due to the increasing size of the lesion. Female patients might have associated anomalies of the genital tract, including a rectovaginal fistula and vaginal septa. Plain x-rays demonstrate a defect in the sacrum, and CT scanning or MRI outlines the extent of the meningocele and any associated anomalies.

591.4 Myelomeningocele  
Stephen L. Kinsman and Michael V. Johnston

Myelomeningocele represents the most severe form of dysraphism, a so-called aperta or open form, involving the vertebral column and spinal cord, which occurs with an incidence of approximately 1 in 4,000 live births.

ETIOLOGY

The cause of myelomeningocele is unknown, but as with all neural tube closure defects, including anencephaly, a genetic predisposition exists; the risk of recurrence after 1 affected child is 3-4% and increases to 10% with 2 prior affected children. Both epidemiologic evidence and the presence of substantial familial aggregation of anencephaly, myelomeningocele, and craniorachischis indicate heredity, on a polygenic basis, as a significant contributor to the etiology of NTDs. Nutritional and environmental factors have a role in the etiology of myelomeningocele as well.

Folate is intricately involved in the prevention and etiology of NTDs. Folate functions in single-carbon transfer reactions and exists in many chemical forms. Folic acid (pteroylmonoglutamic acid), which is the most oxidized and stable form of folate, occurs rarely in food but is the form used in vitamin supplements and in fortified food products, particularly flour. Most naturally occurring folates (food folate) are pteroypolyglutamates, which contain 1-6 additional glutamate molecules joined in a peptide linkage to the γ-carboxyl of glutamate. Folate coenzymes are involved in DNA synthesis, purine synthesis, generation of formate into the formate pool, and amino acid interconversion; the conversion of homocysteine to methionine provides methionine for the synthesis of S-adenosylmethionine (SAME, an agent important for in vivo methylation). Mutations in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningomyelocele. These enzymes include 5,10-methylenetetrahydrofolate reductase, cystathionine β-synthase, and methionine synthase. An association between a thermolabile variant of 5,10-methylenetetrahydrofolate reductase and mothers of children with NTDs might account for up to 15% of preventable NTDs. Maternal periconceptional use of folic acid supplementation reduces the incidence of NTDs in pregnancies at risk by at least 50%. To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th wk of gestation, when neural tube closure is complete. The mechanisms by which folic acid prevents NTDs remain poorly understood.

PREVENTION

The U.S. Public Health Service has recommended that all women of childbearing age and who are capable of becoming pregnant take 0.4 mg of folic acid daily. If, however, a pregnancy is planned in high-risk women (previously affected child), supplementation should be started with 4 mg of folic acid daily, beginning 1 mo before the time of the planned conception. The modern diet provides about half the daily requirement of folic acid. To increase folic acid intake, fortification of flour, pasta, rice, and cornmeal with 0.15 mg folic acid per 100 g was mandated in the United States and Canada in 1998. The added folic acid is insufficient to maximize the prevention of preventable NTDs. Therefore, informative educational programs and folic acid vitamin supplementation remain essential for women planning a pregnancy and possibly for all women of childbearing age. In addition, women should also strive to consume food folate from a varied diet. Certain drugs, including drugs that antagonize folic acid, such as trimethoprim and the anticonvulsants carbamazepine, phenytoin, phenobarbital, and primidone, increase the risk of myelomeningocele. The anticonvulsant valproic acid causes NTDs in approximately 1-2% of pregnancies when administered during pregnancy. Some epilepsy clinicians recommend that all female patients of childbearing potential who take anticonvulsant medications also receive folic acid supplements. There may be a threshold for ideal red blood cell folate levels (900-1,000 nmol/L), which is associated with a markedly reduced risk of NTDs.

CLINICAL MANIFESTATIONS

Myelomeningocele produces dysfunction of many organs and structures, including the skeleton, skin, and gastrointestinal and genitourinary tracts, in addition to the peripheral nervous system and the CNS. A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases. The extent and degree of the neurologic deficit depend on the location of the myelomeningocele and the associated lesions. A lesion in the low sacral region causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function. Newborns with a defect in the midlumbar or high lumbosacral region typically have either a sac-like cystic structure covered by a thin layer of partially epithelialized tissue (Fig. 591-4) or an exposed flat skin.

Figure 591-4 A lumbar myelomeningocele is covered by a thin layer of skin.
neural placode without overlying tissues. When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

Examination of the infant shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy. Thus, a myelomeningocele above the midlumbar region tends to produce lower motor neuron signs because of abnormalities and disruption of the conus medullaris and above spinal cord structures.

Infants with myelomeningocele typically have increased neurologic deficit as the myelomeningocele extends higher into the thoracic region. These infants sometimes have an associated kyphotic gibbus that requires neonatal orthopedic correction. Patients with a myelomeningocele in the upper thoracic or cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus. They can have neurogenic bladder and bowel.

Hydrocephalus in association with a type II Chiari malformation develops in at least 80% of patients with myelomeningocele. Generally, patients with sacral myelomeningocele have a very low risk of hydrocephalus. The possibility of hydrocephalus developing after the neonatal period should always be considered, no matter what the spinal level. Ventricular enlargement may be indolent and slow growing or may be rapid causing a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting in association with an increased head circumference. Approximately 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain (brainstem) dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This Chiari crisis is caused by downward herniation of the medulla and cerebellar tonsils through the foramen magnum, as well as endogenous malformations in the cerebellum and brainstem, causing dysfunction.

TREATMENT
Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with 1 individual (often a pediatrician) acting as the advocate and coordinator of the treatment program. The news that a newborn child has a devastating condition such as myelomeningocele causes parents to feel considerable grief and anger. They need time to learn about the condition and its associated complications and to reflect on the various procedures and treatment plans. A knowledgeable individual in an unhurried and nonthreatening setting must give the parents the facts, along with general prognostic information and management strategies and timelines. If possible, discussions with other parents of children with NTDs are helpful in resolving important questions and issues.

Surgery is often done within a day or so of birth but can be delayed for several days (except when there is a CSF leak) to allow the parents time to begin to adjust to the shock and to prepare for the multiple procedures and inevitable problems that lie ahead. Evaluation of other congenital anomalies and renal function can also be initiated before surgery. Most pediatric centers aggressively treat the majority of infants with myelomeningocele. After repair of a myelomeningocele, most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting, and dislocated hips may require operative procedures.

Careful evaluation and reassessment of the genitourinary system are some of the most important components of the management. Teaching the parents, and, ultimately, the patient, to regularly catheterize a neurogenic bladder is a crucial step in maintaining a low residual volume and bladder pressure that prevents urinary tract infections and reflux leading to pylonephritis, hydronephrosis, and bladder damage. Latex-free catheters and gloves must be used to prevent development of latex allergy. Periodic urinary cultures and assessment of renal function, including serum electrolytes and creatinine as well as renal scans, vesicourethrogram, renal ultrasonography, and cystometrograms, are obtained according to the risk status and progress of the patient and the results of the physical examination. This approach to urinary tract management has greatly reduced the need for urologic diversionary procedures and significantly decreased the morbidity and mortality associated with progressive renal disease in these patients. Some children can become continent with surgical implantation of an artificial urinary sphincter (these are used less often) or bladder augmentation at a later age.

Although incontinence of fecal matter is common and is socially unacceptable during the school years, it does not pose the same organ-damaging risks as urinary dysfunction, but occasionally fecal impaction and/or meconium develop. Many children can be bowel-trained with a regimen of timed enemas or suppositories that allows evacuation at a predetermined time once or twice a day. Special attention to low anorectal tone and enema administration and retention is often required. Appendicostomy for antegrade enemas may also be helpful (see Chapter 23.4).

Functional ambulation is the wish of each child and parent and may be possible, depending on the level of the lesion and on intact function of the iliofemoral muscles. Almost every child with a sacral or lumbar-sacral lesion obtains functional ambulation; approximately half the children with higher defects ambulate with the use of braces, other orthotic devices, and canes. Ambulation is often more difficult as adolescence approaches and body mass increases. Deterioration of ambulatory function, particularly during earlier years, should prompt referral for evaluation of tethered spinal cord and other neurosurgical issues.

In utero surgical closure of a spinal lesion has been successful in a few centers. Preliminary reports suggest a lower incidence of hindbrain abnormalities and hydrocephalus (fewer shunts) as well as improved motor outcomes. This suggests that the defects may be progressive in utero and that prenatal closure might prevent the development of further loss of function. In utero diagnosis is facilitated by maternal serum AFP screening and by fetal ultrasonography (see Chapter 96).

PROGNOSIS
For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10-15%, and most deaths occur before age 4 yr, although life-threatening complications occur at all ages. At least 70% of survivors have normal intelligence, but learning problems and seizure disorders are more common than in the general population. Previous episodes of meningitis or ventriculitis adversely affect intellectual and cognitive function. Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life. Renal dysfunction is one of the most important determinants of mortality.

Bibliography is available at Expert Consult.

591.5 Encephalocele

 Stephen L. Kinsman and Michael V. Johnston

Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect, called cranium bifidum. A cranial meningocele consists of a CSF-filled meningeal sac only, and a cranial encephalocele contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem. Microscopic examination of the neural tissue within an encephalocele often reveals abnormalities. The cranial defect occurs most commonly in the occipital region at or
Bibliography


591.6 Anencephaly

Stephen L. Kinsman and Michael V. Johnston

An anencephalic infant presents a distinctive appearance with a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain, which results from failure of closure of the rostral neuropore, the opening of the anterior neural tube. The primitive brain consists of portions of connective tissue, vessels, and neuroglia. The cerebral hemispheres and cerebellum are usually absent, and only a residue of the brainstem can be identified. The pituitary gland is hypoplastic, and the spinal cord pyramidal tracts are missing owing to the absence of the cerebral cortex. Additional anomalies include folding of the ears, cleft palate, and congenital heart defects in 10-20% of cases. Most anencephalic infants die within several days of birth.

The incidence of anencephaly approximates 1 in 1,000 live births; the greatest incidence is in Ireland, Wales, and Northern China. The recurrence risk is approximately 4% and increases to 10% if a couple has had 2 previously affected pregnancies. Many factors, in addition to genetics, are implicated as a cause of anencephaly, including low socioeconomic status, nutritional and vitamin deficiencies, and a large number of environmental and toxic factors. It is very likely that several noxious stimuli interact on a genetically susceptible host to produce anencephaly. The incidence of anencephaly has been decreasing since the 1990s. Approximately 50% of cases of anencephaly have associated polyhydramnios. Couples who have had an anencephalic infant should have successive pregnancies monitored, including amniocentesis, determination of AFP levels, and ultrasound examination between the 14th and 16th wk of gestation. Prenatal folic acid supplementation decreases the risk of this condition.

591.7 Disorders of Neuronal Migration

Stephen L. Kinsman and Michael V. Johnston

 Disorders of neuronal migration can result in minor abnormalities with little or no clinical consequence (small heterotopia of neurons) or devastating abnormalities of CNS structure and/or function (intellectual disability, seizures, lissencephaly, and schizencephaly, particularly the open-lip form) (Fig. 591-5). One of the most important mechanisms in the control of neuronal migration is the radial glial fiber system that guides neurons to their proper site. Migrating neurons attach to the radial glial fiber and then disengage at predetermined sites to form, ultimately, the precisely designed 6-layered cerebral cortex. Another important mechanism is the tangential migration of progenitor neurons destined to become cortical interneurons. The severity and the extent of the disorder are related to numerous factors, including the timing of a particular insult and a host of environmental and genetic contributors. Some cortical malformations may be from somatic mutations, as exemplified by kinesin gene mutations in patients with pachygyria.

LISSENCEPHALY

Lissencephaly, or agyria, is a rare disorder that is characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure, giving the appearance of a 3-4 mo fetal brain. The condition is probably a result of faulty neuroblast migration during early embryonic life and is usually associated with enlarged lateral ventricles and heterotopias in the white matter. In some forms, there is a 4-layered cortex, rather than the usual 6-layered one, with a thin rim of periventricular white matter and numerous gray heterotopias visible by microscopic examination. Milder forms of lissencephaly also exist.

Figure 591-5 T1-weighted MRI scan demonstrating band heterotopia. A thin layer of white matter (black arrow) lies between the band of heterotopic gray matter and the cortical surface. Failure of cortical organization with lissencephaly is present in both frontal lobes (white arrow).
Bibliography

These infants present with failure to thrive, microcephaly, marked developmental delay, and a severe seizure disorder. Ocular abnormalities are common, including hypoplasia of the optic nerve and microphthalmia. Lissencephaly can occur as an isolated finding, but it is associated with Miller-Dieker syndrome in approximately 15% of cases. These children have characteristic facies, including a prominent forehead, bitemporal hollowing, anteverted nostrils, a prominent upper lip, and micrognathia. Approximately 70% of children with Miller-Dieker syndrome have visible or submicroscopic chromosomal deletions of 17p13.3.

The gene LIS-1 (lissencephaly 1) that maps to chromosome region 17p13.3 is deleted in patients with Miller-Dieker syndrome. CT and MRI scans typically show a smooth brain with an absence of sulci (Fig. 591-6). Doublecortin is an X chromosome gene that causes lissencephaly when mutated in males and subcortical band heterotopia when mutated in females. Other important forms of lissencephaly include the Walker-Warburg variant and other cobblestone cortical malformations.

**SCHIZENCEPHALY**

Schizencephaly is the presence of unilateral or bilateral clefts within the cerebral hemispheres owing to an abnormality of morphogenesis (Fig. 591-7). The cleft may be fused or unfused and, if unilateral and large, may be confused with a porencephalic cyst. Not infrequently, the borders of the cleft are surrounded by abnormal brain, particularly microgyria. MRI is the study of choice for elucidating schizencephaly and associated malformations.

When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control, and microcephalic, with spastic quadripareisis. Some cases of bilateral schizencephaly are associated with septooptic dysplasia and endocrinologic disorders. Unilateral schizencephaly is a common cause of congenital hemiparesis. It remains controversial whether genetic causes of schizencephaly exist. Some gene mutations are seen in cases of familial schizencephaly.

**NEURONAL HETEROTOPIAS**

Subtypes of neuronal heterotopias include periventricular nodular heterotopias, subcortical heterotopia (including band-type), and marginal glioneuronal heterotopias. Intractable seizures are a common feature.

Several genes have been identified that are a cause of these conditions.

**POLYMICROGYRIAS**

Polymicrogyria is characterized by an augmentation of small convolutions separated by shallow enlarged sulci. Epilepsy, including drug-resistant forms, is a common feature. Truncation of the KBP gene has been implicated in a family with multiple members with polymicrogyria.
Agenesis of the corpus callosum consists of a heterogeneous group of disorders that vary in expression from severe intellectual and neurologic abnormalities to the asymptomatic and normally intelligent patient (Fig. 591-8). The corpus callosum develops from the commissural plate that lies in proximity to the anterior neuropore. Either a direct insult to the commissural plate or disruption of the genetic signaling that specifies and organizes this area during early embryogenesis causes agenesis of the corpus callosum.

It is often said that the outcome of agenesis of the corpus callosum is dictated by the company it keeps. When agenesis of the corpus callosum is an isolated phenomenon, the patient may be normal. When it is accompanied by brain anomalies from cell migration defects, such as heterotopias, polymicrogyria, and pachygyria (broad, wide gyri), patients often have significant neurologic abnormalities, including intellectual disability, microcephaly, hemiparesis, diplegia, and seizures.

The anatomic features of agenesis of the corpus callosum are best depicted on MRI or CT scan and include widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect.

Absence of the corpus callosum may be inherited as an X-linked recessive trait or as an autosomal dominant trait and on occasion as an autosomal recessive trait. The condition may be associated with specific chromosomal disorders, particularly trisomy 8 and trisomy 18. Single-gene mutations have also been identified, usually in association with other anomalies. Agenesis of the corpus callosum is also seen in some metabolic disorders (Table 591-2).

Aicardi syndrome represents a complex disorder that affects many systems and is typically associated with agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Patients are almost all female, suggesting a genetic abnormality of the X chromosome (it may be lethal in males during fetal life). Seizures become evident during the 1st few mo and are typically resistant to anticonvulsants. An electroencephalogram shows independent activity recorded from both hemispheres as a result of the absent corpus callosum and shows often hemihypsarrhythmia. All patients have severe intellectual disability and can have abnormal vertebrae that may be fused or only partially developed (hemivertebra). Abnormalities of the retina, including circumscribed pits or lacunae and coloboma of the optic disc, are the most characteristic findings of Aicardi syndrome.

Colpocephaly refers to an abnormal enlargement of the occipital horns of the ventricular system and can be identified as early as the fetal period. It is often associated with agenesis of the corpus callosum, but it can occur in isolation. It is also associated with microcephaly. It can also be seen in anatomic megalencephaly, such as is associated with Sotos syndrome.

**HOLOPROSENCEPHALY**

Holoprosencephaly is a developmental disorder of the brain that results from defective formation of the prosencephalon and
Bibliography
Disorders Associated with Agenesis of the Corpus Callosum*

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*Reliable incidence data are unavailable for these very rare syndromes.

†Gene symbols in parentheses.

4p−, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl cotransporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1B.


Inadequate induction of forebrain structures. The abnormality, which represents a spectrum of severity, is classified into 3 groups: alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality (Fig. 591-9). A fourth type, the middle interhemispheric fusion variant or syntelencephaly, involves a segmental area of noncleavage, actually a nonseparation, of the posterior frontal and parietal lobes. Facial abnormalities, including cyclopia, synophthalmia, cebocephaly, single nostril, choanal atresia, solitary central incisor tooth, and premaxillary agenesis are common in severe cases, because the prechondral mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. Milder facial abnormalities are seen in milder forms. Alobar holoprosencephaly is characterized by a single ventricle, an absent falx, and nonseparated deep cerebral nuclei. Care must be taken not to overdiagnose holoprosencephaly based on ventricular abnormalities alone. Evidence of nonseparated midline deep-brain structures, such as caudate, putamen, globus pallidus, and hypothalamus, is the critical element for diagnosis.

Affected children with the alobar type have high mortality rates, but some live for years. Mortality and morbidity with milder types are more variable, and morbidity is less severe. Care must be taken not to prognosticate severe outcomes in all cases. The incidence of holoprosencephaly ranges from 1 in 5,000-16,000 live births. A prenatal diagnosis can be confirmed by ultrasonography after the 10th wk of gestation for more severe types, but fetal MRI at later gestational ages gives far greater anatomic, and therefore diagnostic, precision.

The cause of holoprosencephaly is often not identified. There appears to be an association with maternal diabetes. Chromosomal abnormalities, including deletions of chromosomes 7q and 3p, 21q, 2p, 18p, and 13q, as well as trisomy 13 and 18, account for upwards of 50% of all cases. Mutations in the sonic hedgehog gene at 7q have been shown to cause holoprosencephaly. Gene Reviews lists 14 single-gene causes. Clinically, it is important to look for associated anomalies, because many syndromes are associated with holoprosencephaly.

Bibliography is available at Expert Consult.
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591.9 Agenesis of the Cranial Nerves and Dysgenesis of the Posterior Fossa

Classification of disorders of cranial nerve, brainstem, and cerebellum development remains anatomic, but future classification systems will likely be based on the molecular biology of brain development based on the genes involved and the roles they play in orchestrating brain architecture.

**CONGENITAL CRANIAL DYSINNERVATION DISORDERS**

Absence of the cranial nerves or the corresponding central nuclei has been described in several conditions and includes the optic nerve defects, congenital ptosis, Marcus Gunn phenomenon (sucking jaw movements causing simultaneous eyelid blinking; this congenital synkinesis results from abnormal innervation of the trigeminal and oculomotor nerves), trigeminal and auditory nerves defects, and cranial nerves IX, X, XI, and XII defects. Increased understanding of these disorders and their genetic causes has led to the term congenital cranial dysinnervation disorders.

Optic nerve hypoplasia can occur in isolation or as part of the septooptic dysplasia complex (de Morsier syndrome). Septooptic dysplasia can be caused by a mutation in the HESXI gene.

Möbius syndrome is characterized by bilateral facial weakness, which is often associated with paralysis of the abducens nerve. Hypoplasia or agenesis of brainstem nuclei, as well as absent or decreased numbers of muscle fibers, has been reported. Affected infants present in the newborn period with facial weakness, causing feeding difficulties owing to a poor suck. The immobile, dull facies might give the incorrect impression of intellectual impairment; the prognosis for normal development is excellent in most cases. The facial appearance of Möbius syndrome has been improved by facial surgery.

Duane retraction syndrome is characterized by congenital limitation of horizontal globe movement and some globe retraction on attempted adduction and is believed to be the result of abnormal innervation by the oculomotor nerve of the lateral rectus muscle. Abnormalities of cranial nerve development have been demonstrated in this condition.

Less common than Duane retraction syndrome and Möbius syndrome are the group of disorders known as congenital fibrosis of the extraocular muscles. Congenital fibrosis of the extraocular muscles is characterized by severe restriction of eye movements and ptosis from normal oculomotor and trochlear nerve development and/or from abnormalities of extraocular muscle innervation.

**BRAINSTEM AND CEREBELLAR DISORDERS**

Disorders of the posterior fossa structures include abnormalities of not only the brainstem and cerebellum, but also the CSF spaces. Commonly encountered malformations include Chiari malformation, Dandy-Walker malformation, arachnoid cysts, mega cisterna magna, persisting Blake pouch, Joubert syndrome, rhombencephalosynapsis, Lhermitte-Duclos disease, and the pontocerebellar hypoplasias.

Chiari malformation is the most common malformation of the posterior fossa and hindbrain. It consists of herniation of the cerebellar tonsils though the foramen magnum. Often, there is also an associated developmental abnormality of the bones of the skull base leading to a small posterior fossa. Cases can be either asymptomatic or symptomatic. When symptoms develop, they often do not do so until late childhood. Symptoms include headaches that are worse with straining and other maneuvers that increase intracranial pressure. Symptoms of brainstem compression such as dysphagia, oropharyngeal dysfunction, spasticity, tinnitus, and vertigo can often occur. Obstructive hydrocephalus and/or syringomyelia can also occur.

Dandy-Walker malformation is part of a continuum of posterior fossa anomalies that include cystic dilation of the fourth ventricle, hypoplasia of the cerebellar vermis, hydrocephalus, and an enlarged posterior fossa with elevation of the lateral venous sinuses and the tentorium. Extracranial anomalies are also seen. Variable degrees of neurologic impairment are usually present. The etiology of Dandy-Walker malformation includes chromosomal abnormalities, single gene disorders, and exposure to teratogens.

Arachnoid cysts of the posterior fossa can be associated with hydrocephalus. Mega cisterna magna is characterized by an enlarged CSF space inferior and dorsal to the cerebellar vermis and when present in isolation may be considered a normal variant. Persisting Blake pouch is a cyst that obstructs the subarachnoid space and is associated with hydrocephalus.

Joubert syndrome is an autosomal recessive disorder (ciliopathy) with significant genetic heterogeneity that is associated with cerebellar vermis hypoplasia and the pontomesencephalic molar tooth sign (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles) (Fig. 591-10). It is associated with hypotonia, ataxia (as toddler), characteristic breathing abnormalities including episodic apnea and hyperpnea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis, and oculomotor apraxia. There can be many associated systemic features (Joubert syndrome and related disorders) including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue (Fig. 591-11).

Rhombencephalosynapsis is an absent or small vermis associated with a nonseparation or fusion of the deep midline cerebellar structures. Ventriculomegaly or hydrocephalus is often seen. There is variable clinical presentation from normal to cognitive and language impairments, epilepsy, and spasticity. Lhermitte-Duclos disease is a dysplastic gangliocytoma of the cerebellum leading to focal enlargement of the cerebellum and macrocephaly, cerebellar signs, and seizures.

Pontocerebellar hypoplasias are a group of disorders characterized by impairment of cerebellar and pontine development together with histopathologic features of neuronal death and glial replacement. Clinical features tend to be nonspecific and include hypotonia, feeding difficulties, developmental delay, and breathing difficulties. Classification, associations, and causes include type I (with features of anterior
Neuroimaging findings in a 2-yr-old child with pure Joubert syndrome (upper panels) compared to a healthy control (lower panels). A, Parasagittal T1-weighted image shows the thickened, elongated, and horizontally orientated superior cerebellar peduncles (white arrow). B, Midsagittal T1-weighted image demonstrates a moderate hypoplasia and dysplasia of the cerebellar vermis (white arrows) with secondary distortion and enlargement of the fourth ventricle with rostral shifting of the fastigium (white arrowhead). A deepened interpeduncular fossa is also noted. C, Axial T1-weighted image at the level of the pontomesencephalic junction shows the molar tooth sign with a deepened interpeduncular fossa (white arrowhead) and elongated, thickened, and horizontally orientated superior cerebellar peduncles (white arrows). Additionally, the cerebellar vermis appears to be hypoplastic and its remnants dysplastic. D, Coronal T1-weighted image reveals the thickened superior cerebellar peduncles (white arrows). (From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol 12:894–905, 2013, Fig. 1.)

Spectrum of organ involvement in Joubert syndrome and classification in clinical subgroups (in bold). Chorioretinal colobomas are more frequently found in the subgroup of Joubert syndrome with liver involvement but can be present also in other subgroups. Similarly, polydactyly (especially if preaxial or mesoaxial) is invariably present in the Orofaciodigital type VI subgroup, but postaxial polydactyly is frequently observed also in association with other Joubert syndrome phenotypes. Other clinical features outside the circles occur more rarely, without a specific association to a clinical subgroup. CNS, central nervous system; COR, cerebello oculorenal; K, kidney involvement; L, liver involvement; MTS, molar tooth sign; OFDVI, orofaciodigital type VI syndrome. (From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol 12:894–905, 2013, Fig. 3.)
Although there are many causes of microcephaly, abnormalities in neuronal migration during fetal development, including heterotopias of neuronal cells and cytoarchitectural derangements, are often found. Microcephaly may be subdivided into 2 main groups: primary (genetic) microcephaly and secondary (nongenetic) microcephaly. A precise diagnosis is important for genetic counseling and for prediction for future pregnancies.

**Etiology**

Primary microcephaly refers to a group of conditions that usually have no associated malformations and follow a mendelian pattern of inheritance or are associated with a specific genetic syndrome. Affected infants are usually identified at birth because of a small head circumference. The more common types include familial and autosomal dominant microcephaly and a series of chromosomal syndromes that are summarized in Table 591-3. Primary microcephaly is also associated with at least 7 gene loci, and 7 single etiologic genes have been identified. It is known as autosomal recessive primary microcephaly and has autosomal inheritance. Many X-linked causes of microcephaly are caused by gene mutations that lead to severe structural brain development anomalies. These are usually not associated with other malformations. Secondary microcephaly is often associated with other anomalies, and the etiology is much more varied. There is a wide range of causes responsible for microcephaly, each with its own characteristic findings.

### Table 591-3 Causes of Microcephaly

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>CHARACTERISTIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY (GENETIC)</strong></td>
<td></td>
</tr>
<tr>
<td>Familial (autosomal recessive)</td>
<td>Incidence 1 in 40,000 live births</td>
</tr>
<tr>
<td></td>
<td>Typical appearance with slanted forehead, prominent nose and ears; severe mental retardation and prominent seizures; surface convolutional markings of the brain, poorly differentiated and disorganized cytoarchitecture</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears</td>
</tr>
<tr>
<td>Syndromes</td>
<td>Normal linear growth, seizures readily controlled, and mild or borderline mental retardation</td>
</tr>
<tr>
<td>Down (trisomy 21)</td>
<td>Incidence 1 in 800 live births</td>
</tr>
<tr>
<td></td>
<td>Abnormal rounding of occipital and frontal lobes and a small cerebellum; narrow superior temporal gyrus, propensity for Alzheimer neurofibrillary alterations, ultrastructural abnormalities of cerebral cortex</td>
</tr>
<tr>
<td>Edward (trisomy 18)</td>
<td>Incidence 1 in 6,500 live births</td>
</tr>
<tr>
<td></td>
<td>Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease, increased gyri, heterotopias of neurons</td>
</tr>
<tr>
<td>Cri-du-chat (5p-)</td>
<td>Incidence 1 in 50,000 live births</td>
</tr>
<tr>
<td></td>
<td>Round facies, prominent epicantonic folds, low-set ears, hypertelorism, characteristic cry</td>
</tr>
<tr>
<td>Cornelia de Lange</td>
<td>Prenatal and postnatal growth delay; synophrys; thin, downturned upper lip proximally placed thumb</td>
</tr>
<tr>
<td>Rubinstein-Taybi</td>
<td>Beaked nose, downward slanting of palpebral fissures, epicantonic folds, short stature, broad thumbs and toes</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz</td>
<td>Ptosis, scaphocephaly, inner epicantonic folds, antverted nostrils</td>
</tr>
<tr>
<td></td>
<td>Low birthweight, marked feeding problems</td>
</tr>
<tr>
<td><strong>SECONDARY (NONGENETIC)</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital infections</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, seizures</td>
</tr>
<tr>
<td></td>
<td>Central nervous system calcification and microgyria</td>
</tr>
<tr>
<td>Rubella</td>
<td>Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, deafness</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations</td>
</tr>
<tr>
<td>Drugs</td>
<td>Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification</td>
</tr>
<tr>
<td>Fetal alcohol</td>
<td>Growth retardation, ptosis, absent phallic and hypoplastic upper lip, congenital heart disease, feeding problems, neuroglial heterotopia, disorganization of neurons</td>
</tr>
<tr>
<td>Fetal hydantoin</td>
<td>Growth delay, hypoplasia of distal phalanges, inner epicantonic folds, broad nasal ridge, antverted nostrils</td>
</tr>
<tr>
<td><strong>Other Causes</strong></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>Microcephaly and mental retardation most severe with exposure before 15th wk of gestation</td>
</tr>
<tr>
<td>Meningitis/encephalitis</td>
<td>Cerebral infarcts, cystic cavitation, diffuse loss of neurons</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Controversial cause of microcephaly</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Maternal diabetes mellitus and maternal hyperphenylalaninemia</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Significant fever during 1st 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies</td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td>Pathologic studies show neuronal heterotopias</td>
</tr>
<tr>
<td></td>
<td>Further studies show no abnormalities with maternal fever</td>
</tr>
<tr>
<td></td>
<td>Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI</td>
</tr>
</tbody>
</table>

malformations such as lissencephaly, holoprosencephaly, polymicrogyria, cobblestone dysplasia, neuronal heterotopia, pontocerebellar hypoplasia; these should be sought on MRI. Secondary microcephaly results from a large number of noxious agents that can affect a fetus in utero or an infant during periods of rapid brain growth, particularly the 1st 2 yr of life.

Acquired microcephaly can be seen in conditions such as Rett, Seckel, and Angelman syndromes and in encephalopathy syndromes associated with severe seizure disorders.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

A thorough family history should be taken, seeking additional cases of microcephaly or disorders affecting the nervous system. It is important to measure a patient’s head circumference at birth to diagnose microcephaly as early as possible. A very small head circumference implies a process that began early in embryonic or fetal development. An insult to the brain that occurs later in life, particularly beyond the age of 2 yr, is less likely to produce severe microcephaly. Serial head circumference measurements are more meaningful than a single determination, particularly when the abnormality is minimal. The head circumference of each parent and sibling should be recorded.

Laboratory investigation of a microcephalic child is determined by the history and physical examination. If the cause of the microcephaly is unknown, the mother’s serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant. A karyotype and/or array comparative genomic hybridization study is obtained if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, and additional congenital anomalies. MRI is useful in identifying structural abnormalities of the brain such as lissencephaly, pachygryria, and polymicrogyria, and CT scanning is useful to detect intracerebral calcification. Additional studies include a fasting plasma and urine amino acid analysis; serum ammonia determination; toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) titers as well as HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus. Single-gene mutations as a cause of both primary microcephaly and syndromic microcephaly are being increasingly identified.

**TREATMENT**

Once the cause of microcephaly has been established, the physician must provide accurate and supportive genetic and family counseling. Because many children with microcephaly are also intellectually challenged, the physician must assist with placement in an appropriate program that will provide for maximal development of the child (see Chapter 36).

*Bibliography is available at Expert Consult.*

### 591.11 Hydrocephalus

*Stephen L. Kinsman and Michael V. Johnston*

Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma (Table 591-4). Because megalencephaly is often discovered as part of an evaluation for hydrocephalus in children with macrocephaly, it is included in this section.

**PHYSIOLOGY**

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originates from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child, approximately 20 mL/hr of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages; through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion, the CSF.

CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mm H₂O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mm H₂O. Normally, CSF flows from the lateral ventricles through the foramina of Monro into the 3rd ventricle. It then traverses the narrow aqueduct of Sylvius, which is approximately 3 mm long and 2 mm in diameter in a child, to enter the 4th ventricle. The CSF exits the 4th ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain. Hydrocephalus resulting from obstruction within the ventricular system is called obstructive or noncommunicating hydrocephalus. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called nonobstructive or communicating hydrocephalus.

**PATHOPHYSIOLOGY AND ETIOLOGY**

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct of Sylvius or a lesion in the 4th ventricle. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with

### Table 591-4 Causes of Hydrocephalus

<table>
<thead>
<tr>
<th>COMMUNICATING</th>
<th>NONCOMMUNICATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
<td>Aqueductal stenosis</td>
</tr>
<tr>
<td>Basilar impression</td>
<td>Infectious*</td>
</tr>
<tr>
<td>Benign enlargement of subarachnoid space</td>
<td>X-linked</td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
<td>Mitochondrial</td>
</tr>
<tr>
<td>Meningeal malignancy</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Posthemorrhagic</td>
<td>L1CAM mutations</td>
</tr>
</tbody>
</table>

Bibliography


branching or forking. In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Rarely, aqueductal stenosis is associated with neurofibromatosis. Aqueductal gliosis can also give rise to hydrocephalus. As a result of neonatal meningitis or a subarachnoid hemorrhage in a premature infant, the ependymal lining of the aqueduct is interrupted and a brisk glial response results in complete obstruction. Intrauterine viral infections can also produce aqueductal stenosis followed by hydrocephalus, and mumps meningoccephalitis has been reported as a cause in a child. A vein of Galen malformation can expand to become large and, because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and the Dandy-Walker syndrome.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can cause obliteration of the cisterns or arachnoid villi and obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus.

**CLINICAL MANIFESTATIONS**

The clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing obstruction, and the duration and rate of increase of the intracranial pressure (ICP). In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and the scalp veins are dilated. The forehead is broad, and the eyes might deviate downward because of impingement of the dilated suprachipineal recess on the brainstem tectum, producing the setting-sun eye sign. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common owing to stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. In an older child, the cranial sutures are less accommodating so that the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age groups, and headache is a prominent symptom in older patients. A gradual change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. With regard to other clinical signs, serial measurements of the head circumference often indicate an increased velocity of growth. Percussion of the skull may produce a cracked pot sound or Macwen sign, indicating separation of the sutures. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests the Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.

**Chiari malformation** consists of 2 major subgroups. Type I typically produces symptoms during adolescence or adult life and is usually not associated with hydrocephalus. Patients complain of recurrent headache, neck pain, urinary frequency, and progressive lower-extremity spasticity. The deformity consists of displacement of the cerebellar tonsils into the cervical canal (Fig. 591-12). Syrinx of the spinal cord, especially the cervical region should be looked for on MRI imaging. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the fourth ventricle during fetal development is responsible. Other theories include tethering of the cord or additional anomalies (syrinx).

The type II Chiari malformation is characterized by progressive hydrocephalus with a myelomenigocele. This lesion represents an anomaly of the hindbrain, probably owing to a failure of pontine flexure development during embryogenesis, and results in elongation of the fourth ventricle and kinking of the brainstem, with displacement of the inferior vermis, pons, and medulla into the cervical canal (Fig. 591-13). Approximately 10% of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by decompression of the posterior fossa. A more indolent form consists of abnormalities of gait, spasticity, and increasing incoordination (including the arms and hands) during childhood.

Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression, but asymptomatic or mildly symptomatic patients may be managed conservatively.

The Dandy-Walker malformation consists of a cystic expansion of the fourth ventricle in the posterior fossa and midline cerebellar hypoplasia, which results from a developmental failure of the roof of the fourth ventricle during embryogenesis (Fig. 591-14). Approximately 90% of patients have hydrocephalus, and a significant number of children have associated anomalies, including agenesis of the posterior cerebellar vermis and corpus callosum. Infants present with a rapid increase in head size and a prominent occiput. Transillumination of the skull may be positive. Most children have evidence of long-tract signs, cerebellar ataxia, and delayed motor and cognitive milestones, probably due to the associated structural anomalies. The Dandy-Walker malformation is managed by shunting the cystic cavity (and on occasion the ventricles as well) in the presence of hydrocephalus.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueductal stenosis. A past history of prematurity with intracranial...
hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of hair, lipoma, or angioma that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation. Transillumination of the skull is positive with massive dilation of the ventricular system or in the Dandy-Walker syndrome. Inspection of the eyegrounds is mandatory because the finding of chorioretinitis suggests an intrauterine infection, such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate as a result of the increased pressure.

Plain skull films typically show separation of the sutures, erosion of the posterior clinoids in an older child, and an increase in convolutional markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP. The CT scan and/or MRI along with ultrasonography in an infant are the most important studies to identify the specific cause and severity of hydrocephalus.

The head might appear enlarged (and can be confused with hydrocephalus) secondary to a thickened cranium resulting from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. MRI has revealed the common occurrence of benign external hydrocephalus, a growth-limited condition where intervention is rarely required. Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), the aminoacidurias (maple syrup urine disease), and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease). In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes and neurofibromatosis are characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of parents’ head circumferences is necessary to establish the diagnosis.

Figure 591-14 Dandy-Walker cyst. A, Axial CT scan (preoperative) showing large posterior fossa cyst (Dandy-Walker cyst; large arrows) and dilated lateral ventricles (small arrows), a complication secondary to cerebrospinal fluid (CSF) pathway obstruction at the fourth ventricular outlet. B, Same patient, with a lower axial CT scan showing splaying of the cerebellar hemispheres by the dilated fourth ventricle (Dandy-Walker cyst). The dilated ventricles proximal to the fourth ventricle again show CSF obstruction caused by the Dandy-Walker cyst. C, MRI of the same patient showing decreased size of the Dandy-Walker cyst and temporal horns (arrows) after shunting. The incomplete vermis (small arrow) now becomes recognizable.
MEGALENCEPHALY

Megalencephaly is an anatomic disorder of brain growth defined as a brain weight >98th percentile for age (or ≥2 SD above the mean) that is usually accompanied by macrocephaly (an occipitofrontal circumference >98th percentile). Various structural and degenerative diseases are associated with megalencephaly, but anatomic and genetic causes exist as well. The most common cause of anatomic megalencephaly is benign familial megalencephaly. This condition is easily diagnosed by careful family history and measurement of the parents’ head circumferences (occipitofrontal circumferences). On the other hand, macrocephaly is a known feature of more than 100 syndromes.

Anatomic megalencephaly is usually apparent at birth, and head growth continues to run parallel to the upper percentiles. Sometimes, in some syndromes, increased occipitofrontal circumference is the presenting sign. Neuroimaging is critical in identifying the various structural and gyral abnormalities seen in syndromic macrocephaly and determining whether anatomic megalencephaly exists.

Common megalencephaly-associated macrocephaly syndromes include syndromes with prenatal and/or postnatal somatic overgrowth such as Sotos, Simpson-Golabi-Behmel, fragile X, Weaver, macrocephaly-maronita telangiectatica congenita, and Bannayan-Ruvalcaba-Riley syndromes, and syndromes without somatic overgrowth such as FG, Greig cephalopolysyndactyly, acrocallosal, and Gorlin.

Sotos syndrome (cerebral gigantism) is the most common megalencephalic syndrome, with 50% of patients having macrocephaly and 100% of patients having macrocephaly by age 1 yr. Early postnatal overgrowth normalizes by adulthood. Facial features include high forehead with frontal bossing, sparse hair in the frontoparietal region, downsloping palpebral fissures, apparent hypertelorism, long narrow face, prominent mandible, and malar flushing. Hypotonia, poor coordination, and speech delay are common. Most children show cognitive impairment, ranging from mild to severe.

HYDRANENCEPHALY

Hydranencephaly may be confused with hydrocephalus. The cerebral hemispheres are absent or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over the membrane. The midbrain and brainstem are relatively intact (Fig. 591-15).

The cause of hydranencephaly is unknown, but bilateral occlusion of the internal carotid arteries during early fetal development would explain most of the pathologic abnormalities. Affected infants can have a normal or enlarged head circumference at birth that grows at an excessive rate postnatally. Transillumination shows an absence of the cerebral hemispheres. The child is irritable, feeds poorly, develops seizures and spastic quadriaparesis, and has little or no cognitive development. A ventriculoperitoneal shunt prevents massive enlargement of the cranium.

TREATMENT

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt. Endoscopic third ventriculostomy has evolved as a viable approach and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Ventricular shunting may be avoided with this approach. The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by Staphylococcus epidermidis. With meticulous preparation, the shunt infection rate can be reduced to <5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyeleocoele.

PROGNOSIS

Prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Hydrocephalic children are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP. The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus. Although most hydrocephalic children are pleasant and mild mannered, some children show aggressive and delinquent behavior. Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele is relatively common, possibly because of increased gonadotropin secretion in response to increased ICP. It is imperative that hydrocephalic children receive long-term follow-up in a multidisciplinary setting.

Bibliography is available at Expert Consult.

591.12 Craniosynostosis

Stephen L. Kinsman and Michael V. Johnston

Craniosynostosis is defined as premature closure of the cranial sutures and is classified as primary or secondary. It is associated with varying types of abnormal skull shape. Primary craniosynostosis refers to closure of 1 or more sutures owing to abnormalities of skull development, whereas secondary craniosynostosis results from failure of brain growth and expansion and is not discussed here. The incidence of primary craniosynostosis approximates 1 in 2,000 live births. The cause is unknown in the majority of children; however, genetic syndromes account for 10-20% of cases. Deformational forces appear important in occipital and frontal plagiocephaly in many cases. Early detection of posterior skull shape is critical and allows successful intervention to be offered in the form of physical therapy for torticollis and other positional asymmetries that lead to plagiocephaly.
Bibliography


**DEVELOPMENT AND ETIOLOGY**

The bones of the cranium are well developed by the 5th mo of gestation (frontal, parietal, temporal, and occipital) and are separated by sutures and fontanels. The brain grows rapidly in the 1st several yr of life and is normally not impeded because of equivalent growth along the suture lines. The cause of craniosynostosis is unknown, but the prevailing hypothesis suggests that abnormal development of the base of the skull creates exaggerated forces on the dura that act to disrupt normal cranial suture development. Genetic factors have been identified for some isolated and for many syndromic causes of craniosynostosis (Table 591-5).

**CLINICAL MANIFESTATIONS AND TREATMENT**

Most cases of craniosynostosis are evident at birth and are characterized by a skull deformity that is a direct result of premature suture fusion. Palpation of the suture reveals a prominent bony ridge, and fusion of the suture may be confirmed by plain skull roentgenograms, CT scan, or bone scan in ambiguous cases (Table 591-6).

Premature closure of the sagittal suture produces a long and narrow skull, or scaphocephaly, the most common form of craniosynostosis. Scaphocephaly is associated with a prominent occiput, a broad forehead, and a small or absent anterior fontanel. The condition is sporadic, is more common in males, and often causes difficulties during labor because of cephalopelvic disproportion. Scaphocephaly does not produce increased ICP or hydrocephalus, and results of neurologic examination of affected patients are normal.

Frontal plagiocephaly is the next most common form of craniosynostosis and is characterized by unilateral flattening of the forehead, elevation of the ipsilateral orbit and eyebrow, and a prominent ear on the corresponding side. The condition is more common in females and is the result of premature fusion of a coronal and sphenofrontal suture. Surgical intervention produces a cosmetically pleasing result. When imaging does not reveal a closed suture, positional factors are of primary importance.

Occipital plagiocephaly is most often a result of positioning during infancy and is more common in an immobile child or a child with a disability, but fusion or sclerosis of the lambdoid suture can cause unilateral occipital flattening and bulging of the ipsilateral frontal bone. Trigonocephaly is a rare form of craniosynostosis caused by premature fusion of the metopic suture. These children have a keel-shaped forehead and hypotelorism and are at risk for associated developmental abnormalities of the forebrain. Milder forms of metopic ridging are more common. Turricephaly refers to a cone-shaped head from premature fusion of the coronal, and often sphenofrontal and frontoethmoidal, sutures. The kleeblattschädel deformity is a peculiarly shaped skull that resembles a cloverleaf. Affected children have very prominent temporal bones, and the remainder of the cranium is constricted. Hydrocephalus is a common complication.

Premature fusion of only 1 suture rarely causes a neurologic deficit. In this situation, the sole indication for surgery is to enhance the child's cosmetic appearance, and the prognosis depends on the suture involved.

**Table 591-5**

Commonly Used Clinical Genetic Classifications of Craniosynostoses

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISOLATED CRANIOSYNOSTOSIS</strong></td>
<td></td>
</tr>
<tr>
<td>Morphologically described</td>
<td>Unknown, uterine constraint, or FGFR3 mutation</td>
</tr>
<tr>
<td>SYNDROMIC CRANIOSYNOSTOSIS</td>
<td></td>
</tr>
<tr>
<td>Antler-Bixler syndrome</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>Usually 1 of 2 mutations in FGFR2</td>
</tr>
<tr>
<td>Beare-Stevenson syndrome</td>
<td>Mutation in FGFR2 or FGFR3</td>
</tr>
<tr>
<td>Baller-Gerold syndrome</td>
<td>Mutation in TWIST heterogenous</td>
</tr>
<tr>
<td>Carpenter syndrome</td>
<td>Unknown</td>
</tr>
<tr>
<td>Craniostenogasia dysplasia</td>
<td>Unknown gene at Xp22</td>
</tr>
<tr>
<td>Crouzon syndrome</td>
<td>Numerous different mutations at FGFR2</td>
</tr>
<tr>
<td>Crouzonmesodermaloskeletal</td>
<td>Mutation in FGFR3</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
</tr>
<tr>
<td>Jackson-Weiss syndrome</td>
<td>Mutation in FGFR2</td>
</tr>
<tr>
<td>Muenke syndrome</td>
<td>Mutation in FGFR3</td>
</tr>
<tr>
<td>Pfeiffer syndrome</td>
<td>Mutation in FGFR1 or numerous</td>
</tr>
<tr>
<td>Saethre-Chotzen syndrome</td>
<td>Mutation in TWIST</td>
</tr>
<tr>
<td>Shprintzen-Goldberg syndrome</td>
<td>Mutation in FBEN1</td>
</tr>
</tbody>
</table>


**Table 591-6**

Epidemiology and Clinical Characteristics of the Common Craniosynostoses

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EPIDEMIOLOGY</th>
<th>SKULL DEFORMITY</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sagittal</td>
<td>Most common CSO affecting a single suture, 80% male</td>
<td>Dolicocephaly or scaphocephaly (boat-shaped)</td>
<td>Frontal bossing, prominent occiput, palpable keel ridge. OFC normal and reduced biparietal diameter</td>
</tr>
<tr>
<td>Coronal</td>
<td>18% of CSO, more common in girls Associated with Apert syndrome (with syndactyly) and Crouzon disease, which includes abnormal sphenoid, orbital, and facial bones (hypoplasia of the midface)</td>
<td>Unilateral: plagiocephaly Bilateral: brachycephaly, acrocephaly</td>
<td>Unilateral: flattened forehead on affected side, flat checks, nose deviation on normal side; higher supraorbital margin leading to harlequin sign on radiograph and outward rotation of orbit can result in ambylophia Bilateral: broad, flattened forehead. In Apert syndrome accompanied by syndactyly and in Crouzon disease by hypoplasia of the midface and progressive proptosis</td>
</tr>
<tr>
<td>Lambdoid</td>
<td>10-20% of CSO, M:F ratio 4:1</td>
<td>Lambdoid/occipital plagiocephaly; right side affected in 70% of cases</td>
<td>Unilateral: flattening of occiput, indentation along synostotic suture, bulging of ipsilateral forehead leading to rhomboid skull, ipsilateral ear is anterior and inferior Bilateral: brachycephaly with bilateral anteriorly and inferiorly displaced ears</td>
</tr>
<tr>
<td>Metopic</td>
<td>Association with 19p chromosome abnormality</td>
<td>Trigonocephaly</td>
<td>Pointed forehead and midline ridge, hypotelorism</td>
</tr>
<tr>
<td>Multiple</td>
<td>Oxycephaly</td>
<td>Tower skull with undeveloped sinuses and shallow orbits, and elevated intercranial pressure</td>
<td></td>
</tr>
</tbody>
</table>

CSO, craniosynostosis; OFC, occipital-frontal circumference.

and on the degree of disfigurement. Neurologic complications, including hydrocephalus and increased ICP, are more likely to occur when 2 or more sutures are prematurely fused, in which case operative intervention is essential. The role of early repositioning efforts and therapy for torticollis and the use of cranial molding devices are beyond the scope of this review.

The most prevalent genetic disorders associated with craniosynostosis include Crouzon, Apert, Carpenter, Chotzen, and Pfeiffer syndromes. Crouzon syndrome is characterized by premature craniosynostosis and is inherited as an autosomal dominant trait. The shape of the head depends on the timing and order of suture fusion but most often is a compressed back-to-front diameter or brachycephaly resulting from bilateral closure of the coronal sutures. The orbits are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features.

Apert syndrome has many features in common with Crouzon syndrome. Apert syndrome is usually a sporadic condition, although autosomal dominant inheritance can occur. It is associated with premature fusion of multiple sutures, including the coronal, sagittal, squamosal, and lambdoid sutures. The facies tend to be asymmetric, and the eyes are less proptotic than in Crouzon syndrome. Apert syndrome is characterized by syndactyly of the 2nd, 3rd, and 4th fingers, which may be joined to the thumb and the 5th finger. Similar abnormalities often occur in the feet. All patients have progressive calcification and fusion of the bones of the hands, feet, and cervical spine.

Carpenter syndrome is inherited as an autosomal recessive condition, and the many fusions of sutures tend to produce the kleeblattschädel skull deformity. Soft tissue syndactyly of the hands and feet is always present, and intellectual disability is common. Additional but less common abnormalities include congenital heart disease, corneal opacities, coxa valga, and genu valgum.

Chotzen syndrome is characterized by asymmetric craniosynostosis and plagiocephaly. The condition is the most prevalent of the genetic syndromes and is inherited as an autosomal dominant trait. It is associated with facial asymmetry, ptosis of the eyelids, shortened fingers, and soft tissue syndactyly of the 2nd and 3rd fingers.

Pfeiffer syndrome is most often associated with turriencephaly. The eyes are prominent and widely spaced, and the thumbs and great toes are short and broad. Partial soft-tissue syndactyly may be evident. Most cases appear to be sporadic, but autosomal dominant inheritance has been reported.

Mutations of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with phenotypically specific types of craniosynostosis. Mutations of the FGFR1 gene located on chromosome 8 result in Pfeiffer syndrome; a similar mutation of the FGFR2 gene causes Apert syndrome. Identical mutations of the FGFR2 gene can result in both Pfeiffer and Crouzon phenotypes.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased ICP, papilledema, optic atrophy resulting from abnormalities of the optic foramina, respiratory problems secondary to a deviated nasal septum or choanal atresia, and disorders of speech and deafness. Cranietomy is mandatory for management of increased ICP, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants.

Bibliography is available at Expert Consult.
Bibliography


Deformational plagiocephaly (DP), also known as positional plagiocephaly, is the development of cranial flattening and asymmetry in the infant as a result of extrinsic molding forces placed on the skull, such as consistently sleeping on the same area of the head. Since the suggestion to place sleeping infants on their backs to sleep for the prevention of the sudden infant death syndrome, the incidence of DP has risen dramatically, and this has caused concern for parents and clinicians in the primary care setting.

**Epidemiology and Etiology**

**Incidence**

The incidence is frequent at 6 wk of age (16%), greatest at 4 mo of age (up to 20%), and then decreases over the next 3 yr (7% at 12 mo and 3.3% at 24 mo). It generally resolves completely by 2-3 yr of age. The American Academy of Pediatrics started a campaign in the 1990s that resulted in the recommendation to place infants on their backs or sides while sleeping, which resulted in a 40% decrease in sudden infant death syndrome cases. Within 4 yr, craniofacial centers and primary care offices reported a 600% increase in referrals for plagiocephaly, which was previously reported to be approximately 1 in 300 infants. This may be a result of increasing awareness or early referral, as point prevalence has not changed in the past 40 yr.

Infants cannot reposition their heads in the 1st few wk of life and are not able to hold their own heads up until about 4 mo of age. It is for this reason that DP is most severe around 4 mo of age. It is also during this time that an infant's head circumference is rapidly increasing: about 2 cm/month in the 1st 3 mo, 1 cm/month from 4-6 mo of age, and 0.5 cm/month after 6 mo of age. Around 6 mo of age, an infant has developed head control, and this ability to actively reposition their own head allows for the gradual improvement of the cranial shape because of pressure unloading and continued brain growth.

**Risk Factors**

Congenital torticollis, positional preference when sleeping, and lower levels of activity are especially prominent in patients with DP. Table 592-1 delineates other risk factors. Many of these risk factors cannot be prevented, but sleeping supine with the head always turned to the same side has been found to predict DP independent of the other factors, and this can be prevented. There may be an association between developmental delay and DP. Although not causal, studies have found significant differences in gross motor development such as sitting up, crawling, and rolling back to side, between babies with and without DP.

<table>
<thead>
<tr>
<th>Table 592-1</th>
<th>Factors That Increase Risk for Deformational Plagiocephaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Firstborn child</td>
</tr>
<tr>
<td></td>
<td>Limited passive neck rotation at birth (e.g., congenital torticollis)</td>
</tr>
<tr>
<td></td>
<td>Developmental delay</td>
</tr>
<tr>
<td></td>
<td>Sleep position is supine at birth and at 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Bottle feeding only</td>
</tr>
<tr>
<td></td>
<td>Tummy time &lt;3 times/day</td>
</tr>
<tr>
<td></td>
<td>Lower activity level, slower milestone achievement</td>
</tr>
<tr>
<td></td>
<td>Sleeping with head to same side, positional preference</td>
</tr>
</tbody>
</table>
PLAGIOCEPHALY AND CRANIOSYNOSTOSIS

BETWEEN DEFORMATIONAL EXAMINATION AND DIFFERENTIATING TREATMENT

Abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out craniosynostosis as a primary cause for cranial asymmetry in infants, as management of this condition is very different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 591.12). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents very similarly to posterior DP.

EXAMINATION AND DIFFERENTIATING BETWEEN DEFORMATIONAL PLAGIOCEPHALY AND CRANIOSYNOSTOSIS

Abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out craniosynostosis as a primary cause for cranial asymmetry in infants, as management of this condition is very different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 591.12). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents very similarly to posterior DP.

### Table 592-2 Important Historical and Physical Factors in the Evaluation of a Patient with Plagiocephaly

<table>
<thead>
<tr>
<th></th>
<th>DEFORMATIONAL</th>
<th>SYNOSTOTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth history</td>
<td>• Intrauterine compression • Firstborn child</td>
<td>• Typically no complications</td>
</tr>
<tr>
<td>Head shape at birth</td>
<td>• Typically normal</td>
<td>• Can be irregular</td>
</tr>
<tr>
<td>Age first noticed shape irregularity</td>
<td>• Usually in 1st few mo of life</td>
<td>• Can be at irregular</td>
</tr>
<tr>
<td>How patient prefers to sleep</td>
<td>• Same side, same position • Same even during naps</td>
<td>• Variable</td>
</tr>
<tr>
<td>Bald spot</td>
<td>• Yes</td>
<td>• No</td>
</tr>
<tr>
<td>Motor development for age</td>
<td>• If age atypical for deformational plagiocephaly, typically slow motor development for age • Torticollis present • History of limited activity or mobility</td>
<td>• Varies depending on presence of concomitant syndrome</td>
</tr>
<tr>
<td>Tummy time</td>
<td>• Decreased</td>
<td>• Suggested time</td>
</tr>
<tr>
<td>Signs/symptoms of increasing intracranial pressure</td>
<td>• No</td>
<td>• Possible</td>
</tr>
</tbody>
</table>

### Table 592-3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

<table>
<thead>
<tr>
<th></th>
<th>DEFORMATIONAL PLAGIOCEPHALY</th>
<th>CRANIOSYNOSTOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>External forces applied to the skull • Prenatal: uterine compression, intrauterine constrained • Postnatal: congenital muscular torticollis</td>
<td>Premature fusion of 1 or more cranial sutures</td>
</tr>
<tr>
<td>Common types</td>
<td>• Lateral • Posterior</td>
<td>• Bilateral coronal • Sagittal • Metopic</td>
</tr>
<tr>
<td>Common distinguishing features</td>
<td>• Normal round head shape at birth • Parallelogram shape to head • Ipsilateral ear anteriorly displaced • No palpable bony ridges</td>
<td>• Can have abnormal head shape at birth • Trapezoid shape to head • Ipsilateral ear posteriorly displaced • Palpable bony ridges</td>
</tr>
<tr>
<td>Management</td>
<td>• Repositioning • Physical therapy • Helmet in some cases</td>
<td>• Surgery • Helmet in some cases</td>
</tr>
</tbody>
</table>

adjacent skull bones separated by a suspected synostotic suture. If the plates do not move relative to each other, then the suspicion for craniosynostosis is raised.

**Verifying neck muscle tone and range of motion** is a key part of the exam because it helps in evaluating motor development and in diagnosing congenital torticollis. Resistance to passive motion raises the concern for torticollis. Decreased tone should prompt further evaluation of motor development. Infants do not gain the muscle control to turn or lift their heads until approximately 4 mo of age, and delays in motor development could increase the infant’s risk of DP at later ages than those at which it usually occurs. Decreased range of motion can also be seen in cervical spine abnormalities, although this is rare. Early recognition of these conditions is critical in treatment, management, and outcome.

Accurate and consistent measurements will help to distinguish etiologies and manage infants presenting with an abnormal-shape skull. Along with the usual head circumference measurements, the clinician should also measure cranial width, length, and transcranial diameter (as shown in Figure 592-2), which is best performed with calipers. These measurements allow the clinician to diagnose, determine severity, and monitor the plagiocephaly.

- **Cranial vault asymmetry**: Ratio of oblique measurements. This is difficult to implement because different physicians and authors propose varying points to use for these measurements
- One technology for the evaluation of the severity and improvement over time of DP is the 3-dimensional photographic system. Advantages of this system include an easy and comfortable ability to image in an unbiased manner. Similarly, the use of laser scanners for the prefabrication scans for helmets is frequently employed by orthotists.

After observations and measurements the clinician can determine the type and severity of the DP (Table 592-4 and Fig. 592-3). For lateral DP, bossing of the occiput occurs opposite the flattened deformity and the ear on the same side as the flat area can be anteriorly displaced. This type of DP is typically associated with infants who have torticollis or a head position preference to 1 side. Transdiagonal diameter is typically abnormal in this type of plagiocephaly, and this measurement is the gold standard for determining severity.

In posterior DP, the occiput is uniformly flattened, temporal bossing can occur, and the ears are normal. It is usually associated with large head size and a history of limited activity or mobility. Cephalic index is increased with posterior DP.

**Time** and accurate exam records can help in management. If deformation is worsening when DP typically begins to demonstrate improving head shape, craniosynostosis should be suspected.

### TREATMENT

#### Prevention

Sleep position should be monitored and varied. Alternating the infant’s head to face the head and foot of the crib on alternate nights will allow the infant to sleep facing into the room without always lying on the same side of the head. Consistently alternating sleeping position early on allows the infant to have equal time on both sides of the occiput, and this will become a pattern the infant is used to. Infants who have
### Table 592-4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

<table>
<thead>
<tr>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FINDINGS</strong></td>
</tr>
<tr>
<td>Occiput (vertex view)</td>
</tr>
<tr>
<td>Ear position (vertex view)</td>
</tr>
<tr>
<td>Face, forehead (anterior, lateral, and vertex views)</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LATERAL DEFORMATIONAL PLAGIOCEPHALY</strong></td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Type IV Malar deformity</td>
</tr>
</tbody>
</table>

Cl, cephalic index (cranial index); TDD, transcranial diameter difference.

---

**Figure 592-3** Types of deformational plagiocephaly. (From Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis. J Pediatr Health Care 26:242–250, 2012, Fig. 1.)
an obvious positional preference to a particular side will take more time and effort in purposefully repositioning them counter to their preference. Parents must be counseled in the benefit of this strategy in preventing bald spots or flat spots that can progress to cranial deformity.

“Tummy time” is the term used to describe the infant’s awake time spent lying on their stomach. The suggested amount of tummy time is 10-15 minutes at least 3 times a day. Reassure parents that sleep is the only time during which the prone position should be avoided, and educate the parents as to the benefits for the infant of awake prone positioning to help progression of motor development.

**Treatment Options**

Cranial asymmetry from DP does not usually spontaneously improve, nor do the more-severe manifestations of facial and ear asymmetry disappear. Once a flat spot develops, it is unlikely that the infant will be able to overcome the pull to lie on the same spot in time to allow for reversal of the asymmetry.

“Watch-and-wait” management is not recommended in infants with DP. Evidence suggests that, at a minimum, repositioning and physiotherapy should be initiated as soon as asymmetry is observed.

Repositioning and physiotherapy (RPPT) include the counseling and teaching for parents as to positional changes and tummy time in their child as well as referral to physical therapy in the case of congenital torticollis. RPPT is the optimal treatment choice for patients younger than 4 mo of age who have mild or moderately severe DP. The earliest types of behavioral modifications can be as simple as increasing tummy time, or repositioning the infant’s crib such that everything interesting in the room is on the side opposite the DP.

Molding therapy (helmet therapy) is the use of an orthotic helmet to promote the resolution of cranial asymmetry while the infant’s head is still rapidly growing. Orthotic helmets do not actively mold the skull; rather, they protect the areas that are flat and allow the child to “grow into” the flat spot. Studies have shown helmet therapy to achieve correction 3 times faster and better than repositioning alone. This therapy is still debated because of its expense, time requirements, coverage and side effects (irritation, rashes, and pressure sores). The most recent studies suggest that combined treatment with helmet therapy and RPPT is the most beneficial management of infants older than 4 mo with severe DP or with worsening of mild/moderate DP trialed on RPPT. Infants with severe DP should be considered for helmet therapy at any age.

Studies suggest helmet therapy should be started for significant DP between 4 and 8 mo and continued for 7-8 mo. Parents should be counseled on the commitment involved in this treatment as helmets need to be worn more than 20 hr a day.

Patients with craniosynostosis require surgery. Sometimes, a molding helmet can be used as an adjunctive therapy after surgery but never as monotherapy.

**OUTCOMES**

Outcomes may be better when helmet therapy is started before 6 mo of age, and infants starting therapy later than that do not achieve the same degree of normal head measurements as those whose helmet therapy is started before 6 mo of age do. Significant improvements in asymmetry are usually obvious at 4-11 wk after initiation of helmet therapy.

Studies in patients with a median follow-up age of 9 yr old found that 75% of cases had a what both parents and patients considered to be a normal head appearance. Nine percent of patients and 4% of parents noted residual asymmetry that they considered significant.

Cognitive and academic outcomes may be different depending on the side of deformity. Poorer academic performance and greater speech abnormalities were found in patients with left-sided deformities compared to those with right-sided deformities. This manifested as double the number of patients with expressive speech abnormalities and triple the number of special education needs. It is unclear what the underlying mechanism is; treatment differences were apparently not a factor.

In general, children with DP and without comorbid conditions are usually developmentally normal, healthy children. This is in contrast to craniosynostosis, in which increases in intracranial pressure may have deleterious effects on central nervous system function.

Bibliography is available at Expert Consult.
Bibliography


A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International Classification of Epileptic Seizures divides epileptic seizures into 2 large categories: In focal (formerly known as partial) seizures, the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of 1 cerebral hemisphere. The term simple partial seizures is an outdated classification that refers to focal seizures with no alteration in consciousness whereas complex partial seizures, currently also referred to as focal dyscognitive, denote focal seizures with altered awareness of the surroundings. In generalized seizures, the first clinical and EEG changes indicate synchronous involvement of all of both hemispheres (Table 593-1). Approximately 30% of patients who have a first afebrile seizure have later epilepsy; the risk is approximately 20% if neurologic exam, EEG, and neuroimaging are normal. Febrile seizures are a separate category. Acute symptomatic seizures occur secondary to an acute problem affecting brain excitability such as electrolyte imbalance. Most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of developing epilepsy from it. An unprovoked seizure is one that is not an acute symptomatic seizure. Remote symptomatic seizure is one that is considered to be secondary to a distant brain injury, such as an old stroke. Reflex seizures are usually precipitated by a sensory stimulus such as flashing lights (see Chapter 593.9).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition. The clinical diagnosis of epilepsy usually requires the occurrence of at least 1 unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences. For epidemiologic and commonly for clinical purposes, epilepsy is considered to be present when 2 or more unprovoked seizures occur in a time frame of longer than 24 hr. Approximately 4-10% of children experience at least 1 seizure (febrile or afebrile) in the 1st 16 yr of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood. The annual prevalence is 0.5-1.0%. Thus, the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. Seizure disorder is a general term that is usually used to include any 1 of several disorders, including epilepsy, febrile seizures, and possibly single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An epileptic syndrome is a disorder that manifests 1 or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished...
Part XXVII  ●  The Nervous System

Table 593-1  Types of Epileptic Seizures

<table>
<thead>
<tr>
<th>SEIZURE TYPE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELF-LIMITED SEIZURE TYPES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Focal Seizures</strong></td>
<td>Focal sensory seizures</td>
</tr>
<tr>
<td></td>
<td>With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)</td>
</tr>
<tr>
<td></td>
<td>With experiential sensory symptoms (e.g., temporoparietaloccipital junction seizures)</td>
</tr>
<tr>
<td><strong>Focal Motor Seizures</strong></td>
<td>With elementary clonic motor signs</td>
</tr>
<tr>
<td></td>
<td>With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)</td>
</tr>
<tr>
<td></td>
<td>With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)</td>
</tr>
<tr>
<td></td>
<td>With hyperkinetic automatisms</td>
</tr>
<tr>
<td></td>
<td>With focal negative myoclonus</td>
</tr>
<tr>
<td></td>
<td>With inhibitory motor seizures</td>
</tr>
<tr>
<td><strong>Gelastic Seizures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemiconvulsive Seizures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondarily Generalized Seizures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generalized Seizures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tonic-Clonic Seizures</strong></td>
<td>Includes variations beginning with a clonic or myoclonic phase</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clonic Seizures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tonic Seizures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myoclonic Seizures</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myoclonic Atonic Seizures</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atonic Seizures</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reflex Seizures in Generalized Epilepsy Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unknown Epileptic Spasms</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONTINUOUS SEIZURE TYPES**

<table>
<thead>
<tr>
<th>SEIZURE TYPE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized Status Epilepticus</strong></td>
<td>Generalized tonic-clonic status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Clonic status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Absence status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Tonic status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Myoclonic status epilepticus</td>
</tr>
<tr>
<td><strong>Focal Status Epilepticus</strong></td>
<td>Epilepsia partialis continua of Kojevnikov</td>
</tr>
<tr>
<td></td>
<td>Aura continua</td>
</tr>
<tr>
<td></td>
<td>Limbic status epilepticus (psychomotor status)</td>
</tr>
<tr>
<td></td>
<td>Hemiconvulsive status with hemiparesis</td>
</tr>
</tbody>
</table>

**PRECIPITATING STIMULI FOR REFLEX SEIZURES**

<table>
<thead>
<tr>
<th>STIMULUS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual stimuli</td>
<td>Flickering light—color to be specified when possible</td>
</tr>
<tr>
<td></td>
<td>Patterns</td>
</tr>
<tr>
<td></td>
<td>Other visual stimuli</td>
</tr>
<tr>
<td>Thinking</td>
<td></td>
</tr>
<tr>
<td>Music</td>
<td></td>
</tr>
<tr>
<td>Eating</td>
<td></td>
</tr>
<tr>
<td>Praxis</td>
<td></td>
</tr>
<tr>
<td>Somatosensory</td>
<td></td>
</tr>
<tr>
<td>Proprioceptive</td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td></td>
</tr>
<tr>
<td>Hot water</td>
<td></td>
</tr>
<tr>
<td>Startle</td>
<td></td>
</tr>
</tbody>
</table>

(Tables 593-2 to 593-5). This classification has to be distinguished from the classification of epileptic seizures that refers to single events rather than to clinical syndromes. In general, seizure type is the primary determinant of the type of medications the patient is likely to respond to, and the epilepsy syndrome determines the type of prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality which is thought to result in cognitive and other impairments in the patient. **Idiopathic epilepsy** is an older term that refers to an epilepsy syndrome that is genetic or presumed genetic and in which there is no underlying disorder affecting development or other neurologic function (e.g., petit mal epilepsy). In the International League Against Epilepsy (ILAE) classification of etiology of epilepsy, idiopathic epilepsy was replaced by the term **genetic epilepsy**, which implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) in which the genetic defect is not causative of a brain structural or metabolic disorder other than the epilepsy. **Symptomatic epilepsy** is also an older term referring to an epilepsy syndrome caused by an underlying brain disorder that may or may not be genetic (e.g., epilepsy secondary to tuberous sclerosis or to an old stroke); this is referred to as **structural/metabolic epilepsy**, which would be caused by a distinct structural or metabolic entity that increases the risk for seizures and causes the epilepsy. The older terms of **cryptogenic epilepsy** or of presumed **symptomatic epilepsy** refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function, but the underlying disorder is not known; this is referred to as the **unknown epilepsy**, designating that the underlying cause of the epilepsy is as yet unknown.

**EVALUATION OF THE FIRST SEIZURE**

Initial evaluation of an infant or child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration. For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures such as meningitis, systemic sepsis, unintentional or nonaccidental intentional head trauma, and ingestion of drugs of abuse or accidental ingestion of drugs or of other toxins. The history should attempt to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child’s postictal state (see Chapter 593.9). Most parents vividly recall their child’s initial convulsion and can describe it in detail.

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** may be characterized by motor or sensory symptoms, which could include forceful turning of the head and eyes to 1 side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesias or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often, but not always, secondary to a
Table 593-2  Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

<table>
<thead>
<tr>
<th>SPECIFIC SYNDROMES</th>
<th>AGE AT ONSET</th>
<th>AGE AT REMISSION</th>
<th>PROGNOSIS</th>
<th>MONOTHERAPY OR ADD-ON</th>
<th>POSSIBLE ADD-ON</th>
<th>SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPILEPSIES OF UNKNOWN CAUSE OF INFANCY AND CHILDHOOD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign infantile seizures (nonfamilial)</td>
<td>Infant</td>
<td>Infant</td>
<td>Good</td>
<td>PB</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
<td>3-13 yr</td>
<td>16 yr</td>
<td>Good</td>
<td>CBZ, LEV, OXC, VPA</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Early and late-onset idiopathic occipital epilepsy</td>
<td>2-8 yr, 6-17 yr</td>
<td>12 yr or younger, 18 yr</td>
<td>Good</td>
<td>CBZ, LEV, OXC, VPA</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td><strong>FAMILIAL (AUTOSOMAL DOMINANT) EPILEPSIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign familial neonatal convulsions</td>
<td>Newborn to young infant</td>
<td>Newborn to young infant</td>
<td>Good</td>
<td>PB</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Benign familial infantile convulsions</td>
<td>Infant</td>
<td>Infant</td>
<td>Good</td>
<td>CBZ, PB</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>Childhood</td>
<td>Variable</td>
<td>CBZ, GBP, OXC, PHT, TPM</td>
<td>CLB, LEV, PB, PHT</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Familial lateral temporal lobe epilepsy</td>
<td>Childhood to adolescence</td>
<td>Variable</td>
<td>CBZ, GBP, OXC, PHT, TPM, VPA</td>
<td>CLB, LEV, PB, PHT</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Generalized epilepsies with febrile seizures plus</td>
<td>Variable</td>
<td>Long lasting</td>
<td>Variable</td>
<td>CBZ, LEV, OXC, TPM, VPA</td>
<td>CLB, LEV, PB, PHT, ZON</td>
<td>No</td>
</tr>
<tr>
<td><strong>STRUCTURAL–METABOLIC FOCAL EPILEPSIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limbic Epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesial temporal lobe epilepsy with hippocampal sclerosis</td>
<td>School-age or earlier</td>
<td>Long lasting</td>
<td>Variable</td>
<td>CBZ, LEV, OXC, TPM, VPA</td>
<td>CLB, GBP, LAC, PB, PHT, ZON</td>
<td>Temporal resection</td>
</tr>
<tr>
<td>Mesial temporal lobe epilepsy defined by specific causes</td>
<td>Variable</td>
<td>Long lasting</td>
<td>Variable</td>
<td>CBZ, LEV, OXC, TPM, VPA</td>
<td>CLB, GBP, LAC, PB, PHT, ZON</td>
<td>Temporal resection</td>
</tr>
<tr>
<td>Other types defined by location and cause</td>
<td>Variable</td>
<td>Long lasting</td>
<td>Variable</td>
<td>CBZ, LEV, OXC, TPM, VPA</td>
<td>CLB, GBP, LAC, PB, PHT, ZON</td>
<td>Lesionectomy ± temporal resection</td>
</tr>
<tr>
<td>Neocortical Epilepsies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen syndrome</td>
<td>6-12 yr</td>
<td>Progressive</td>
<td>Ominous</td>
<td>Plasmapheresis, immunoglobulins</td>
<td>CBZ, LAC, PB, PHT, TPM</td>
<td>Functional hemispherectomy</td>
</tr>
<tr>
<td>Hemiconvulsion-hemiplegia syndrome</td>
<td>1-5 yr</td>
<td>Chronic</td>
<td>Severe</td>
<td>CBZ, LEV, OXC, TPM, VPA</td>
<td>CBZ, GBP, LAC, PB, PHT, ZON</td>
<td>Functional hemispherectomy</td>
</tr>
<tr>
<td>Other types defined by location and cause</td>
<td>Variable</td>
<td>Long lasting</td>
<td>Variable</td>
<td>CBZ, LEV, OXC, TPM, VPA</td>
<td>PHT, PB, CLB, GBP, LAC, ZON</td>
<td>Lesionectomy ± cortical resection</td>
</tr>
<tr>
<td>Migrating partial seizures of early infancy</td>
<td>Infant</td>
<td>No remission</td>
<td>Ominous</td>
<td>Bromides, CBZ, LEV, PB, PHT, TPM, VPA</td>
<td>BDZ, LAC, ZON</td>
<td>No</td>
</tr>
<tr>
<td><strong>GENERALIZED EPILEPSIES OF UNKNOWN CAUSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign myoclonic epilepsy in infancy</td>
<td>3 mo-3 yr</td>
<td>3-5 yr</td>
<td>Variable</td>
<td>LEV, TPM, VPA</td>
<td>BDZ, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Epilepsy with myoclonic atactic seizures</td>
<td>3-5 yr</td>
<td>Variable</td>
<td>ESM, TPM, VPA</td>
<td>BDZ, ketogenic diet, LEV, LTG, steroids, ZON</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Childhood absence epilepsy</td>
<td>5-6 yr</td>
<td>10-12 yr</td>
<td>Good</td>
<td>ESM, LTG, VPA</td>
<td>Acetazolamide, ketogenic diet, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Epilepsy with myoclonic absences</td>
<td>1-12 yr</td>
<td>Variable</td>
<td>Guarded</td>
<td>ESM, VPA</td>
<td>BDZ, ZON</td>
<td>No</td>
</tr>
</tbody>
</table>

*Reflects current trends in practice, which may be off-label and may not be FDA approved for that indication. See Table 593-10 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types.

ACTH, adrenocorticotropic hormone; BDZ, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP: diazepam; ESM, ethosuximide; FBM: felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC: oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; RFD, rufinamide; TPM, topiramate; VGB: vigabatrin; VPA, valproic acid; ZON, zonisamide.
### Table 593-2
Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont’d

<table>
<thead>
<tr>
<th>SPECIFIC SYNDROMES</th>
<th>AGE AT ONSET</th>
<th>AGE AT REMISSION</th>
<th>PROGNOSIS</th>
<th>MONOTHERAPY OR ADD-ON*</th>
<th>POSSIBLE ADD-ON†</th>
<th>SURGERY‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERALIZED EPILEPSIES OF UNKNOWN CAUSE WITH VARIABLE PHENOTYPES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>10-12 yr</td>
<td>Usually lifelong</td>
<td>Good</td>
<td>ESM, LTG, VPA</td>
<td>BDZ</td>
<td>No</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>12-18 yr</td>
<td>Usually lifelong</td>
<td>Good</td>
<td>LEV, TPM, VPA</td>
<td>BDZ, LTG, PB, PRM, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Epilepsy with generalized tonic-clonic seizures only</td>
<td>12-18 yr</td>
<td>Usually lifelong</td>
<td>Good</td>
<td>LEV, LTG, TPM, VPA</td>
<td>BDZ, CBZ, ZON</td>
<td>No</td>
</tr>
<tr>
<td><strong>REFLEX EPILEPSIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic photosensitive occipital lobe epilepsy</td>
<td>10-12 yr</td>
<td>Unclear</td>
<td>Variable</td>
<td>VPA</td>
<td>BDZ, LEV, LTG, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Other visual sensitive epilepsies</td>
<td>2-5 yr</td>
<td>Unclear</td>
<td>Variable</td>
<td>VPA</td>
<td>BDZ, LEV, LTG, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Startle epilepsy</td>
<td>Variable</td>
<td>Long lasting</td>
<td>Guarded</td>
<td>CBZ, GBP, OXC, PHT, TPM, VPA</td>
<td>CLB, LEV, PB, PHT, ZON</td>
<td>Lesionectomy ± cortical resection in some</td>
</tr>
<tr>
<td><strong>EPILEPTIC ENCEPHALOPATHIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early myoclonic encephalopathy and Ohtahara syndrome</td>
<td>Newborn-infant</td>
<td>Poor, Ohtahara syndrome evolves into West syndrome</td>
<td>Ominous</td>
<td>PB, steroids, VGB</td>
<td>BDZ, ZON</td>
<td>No</td>
</tr>
<tr>
<td>WEST SYNDROME</td>
<td>Infant</td>
<td>Variable</td>
<td>Severe</td>
<td>ACTH, steroids, VGB, CLB, stiripentol, TPM, VPA</td>
<td>BDZ, FBM, IVIG, TPM, ZON, BDZ, ZON</td>
<td>Lesionectomy ± cortical resection No</td>
</tr>
<tr>
<td>Dravet syndrome (severe myoclonic epilepsy in infancy)</td>
<td>Infant</td>
<td>No remission</td>
<td>Severe</td>
<td>CLB, LTG, RFD, TPM, VPA</td>
<td>BDZ, FBM, IVIG, steroids, ZON, BDZ, ESM, IVIG, LGT</td>
<td>Callosotomy</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>3-10 yr</td>
<td>No remission</td>
<td>Severe</td>
<td>LEV, nocturnal DZP, steroids, VPA</td>
<td>BDZ, ESM, IVIG, LGT</td>
<td>Multiple subpial transections, rarely lesionectomy No</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>3-6 yr</td>
<td>8-12 yr</td>
<td>Guarded</td>
<td>LEV, nocturnal DZP, steroids, VPA</td>
<td>BDZ, ESM, IVIG, LGT</td>
<td></td>
</tr>
<tr>
<td>Epilepsy with continuous spike waves during slow-wave sleep</td>
<td>4-7 yr</td>
<td>8-12 yr</td>
<td>Guarded</td>
<td>LEV, nocturnal DZP, steroids, VPA</td>
<td>BDZ, ESM, IVIG, LGT</td>
<td></td>
</tr>
<tr>
<td><strong>PROGRESSIVE MYOCLONUS EPILEPSIES</strong></td>
<td>Late infant to adolescent</td>
<td>Progressive</td>
<td>Ominous</td>
<td>TPM, VPA, ZON</td>
<td>BDZ, PB</td>
<td>No</td>
</tr>
<tr>
<td>Unverricht-Lundborg, Lafora, ceroid lipofuscinoses, etc.</td>
<td>Infant</td>
<td>Variable</td>
<td>Severe</td>
<td>LEV, VPA</td>
<td>BDZ, PB</td>
<td>No</td>
</tr>
<tr>
<td><strong>OTHER EPILEPSIES AND SEIZURE DISORDERS OF UNKNOWN OR OTHER CAUSES</strong></td>
<td>Infant</td>
<td>Variable</td>
<td>No remission</td>
<td>LEV, VPA, PB if repeated and prolonged</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Benign neonatal seizures</td>
<td>Newborn</td>
<td>Newborn</td>
<td>Good</td>
<td>LEV, PB</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td>3-5 yr</td>
<td>3-6 yr</td>
<td>Good</td>
<td>PB or VPA if repeated and prolonged</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Reflex seizures</td>
<td>Variable</td>
<td>n/a</td>
<td>Good</td>
<td>LEV, VPA</td>
<td>LTG, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Drug or other chemically induced seizures</td>
<td>Variable</td>
<td>n/a</td>
<td>Good</td>
<td>LEV, VPA</td>
<td>LTG, ZON</td>
<td>No</td>
</tr>
<tr>
<td>Immediate and early posttraumatic seizures</td>
<td>Variable</td>
<td>n/a</td>
<td>Good</td>
<td>LEV, PHT</td>
<td>—</td>
<td>No</td>
</tr>
</tbody>
</table>

### Identified Genes for Epilepsy Syndromes

**Table 593-3**

<table>
<thead>
<tr>
<th>Epilepsy Type</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infantile Onset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign familial neonatal seizures</td>
<td>KCNQ2</td>
<td>Potassium voltage-gated channel</td>
</tr>
<tr>
<td>Benign familial neonatal infantile seizures</td>
<td>SCN2A</td>
<td>Sodium channel protein type 2α</td>
</tr>
<tr>
<td>Early familial neonatal seizures</td>
<td>SCN2A</td>
<td>Sodium channel protein type 2α</td>
</tr>
<tr>
<td>Early infantile epileptic encephalopathy (EIEE)</td>
<td>CDKL5 (EIEE2)</td>
<td>Cyclin-dependent kinase-like 5</td>
</tr>
<tr>
<td></td>
<td>ARX (EIEE1)</td>
<td>Aristaless-related homeobox</td>
</tr>
<tr>
<td></td>
<td>TSC1</td>
<td>Hamartin</td>
</tr>
<tr>
<td></td>
<td>TSC2</td>
<td>Tuberin</td>
</tr>
<tr>
<td></td>
<td>SCN1A (EIEE6)</td>
<td>Sodium channel protein type 2α</td>
</tr>
<tr>
<td></td>
<td>PCDH19 (EIEE9)</td>
<td>Protocadherin-19</td>
</tr>
<tr>
<td></td>
<td>KCNQ2 (EIEE7)</td>
<td>Potassium voltage-gated channel</td>
</tr>
<tr>
<td></td>
<td>STXBP1 (EIEE4)</td>
<td>Syntaxin binding protein 1</td>
</tr>
<tr>
<td></td>
<td>SLC2A1</td>
<td>Solute carrier family 2, facilitated glucose transporter member 1</td>
</tr>
<tr>
<td></td>
<td>ALDH7A1</td>
<td>α-Aminoadipic semialdehyde dehydrogenase (antiquitin)</td>
</tr>
<tr>
<td></td>
<td>POLG</td>
<td>DNA polymerase subunit gamma-1</td>
</tr>
<tr>
<td></td>
<td>SCN2A (EIEE11)</td>
<td>Sodium channel protein type 2α</td>
</tr>
<tr>
<td></td>
<td>PLCB1 (EIEE12)</td>
<td>Phospholipase C β1</td>
</tr>
<tr>
<td></td>
<td>ATP6AP2</td>
<td>Renin receptor</td>
</tr>
<tr>
<td></td>
<td>SPTAN1 (EIEE5)</td>
<td>α-Spectrin</td>
</tr>
<tr>
<td></td>
<td>SLC25A22 (EIEE3)</td>
<td>Mitochondrial glutamate carrier 1</td>
</tr>
<tr>
<td></td>
<td>PNPO</td>
<td>Pyridoxine-5′-phosphate oxidase</td>
</tr>
<tr>
<td></td>
<td>SCN1B</td>
<td>Sodium channel protein type 1α</td>
</tr>
<tr>
<td></td>
<td>SCN2A</td>
<td>Sodium channel protein type 1β</td>
</tr>
<tr>
<td></td>
<td>SCN1A</td>
<td>γ-Aminobutyric acid receptor subunit γ2</td>
</tr>
<tr>
<td></td>
<td>GABRG2</td>
<td>Sodium channel protein type 1α</td>
</tr>
<tr>
<td>Generalized epilepsy with febrile seizures plus (early onset)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood onset epileptic encephalopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood onset epileptic encephalopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized epilepsy with febrile seizures plus (early onset)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy (more commonly presents in adolescence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive myoclonic epilepsy (different forms present from infancy through adulthood)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolecent Onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy (JME)</td>
<td>See Childhood Onset JME</td>
<td></td>
</tr>
<tr>
<td>Progressive myoclonic epilepsy (PME)</td>
<td>See Childhood Onset PME</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)</td>
<td>See Childhood Onset AD-NFLE</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)</td>
<td>See Childhood Onset AD-LTLE</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)</td>
<td>LGI1</td>
<td>Leucine-rich glioma-inactivated protein 1</td>
</tr>
</tbody>
</table>

*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or through exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).
### Table 593-4: Identified Genes for Syndromic Epilepsy Syndromes*

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENE</th>
<th>PROTEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rett/atypical Rett syndromes</td>
<td>MECP2</td>
<td>Methyl CpG binding protein 2</td>
</tr>
<tr>
<td></td>
<td>CJDLS</td>
<td>Cyclin-dependent kinase-like 5</td>
</tr>
<tr>
<td></td>
<td>FOXG1</td>
<td>Forkhead box protein G1</td>
</tr>
<tr>
<td></td>
<td>MBD5</td>
<td>Methyl-CpG-binding domain protein 5</td>
</tr>
<tr>
<td></td>
<td>MEF2C</td>
<td>Myocyte-specific enhancer factor 2C</td>
</tr>
<tr>
<td>Angelman/Angelman-like/Pitt-Hopkins</td>
<td>UBE3A</td>
<td>Ubiquitin protein ligase E3A</td>
</tr>
<tr>
<td>syndromes</td>
<td>SLC9A6</td>
<td>Sodium/hydrogen exchanger 6</td>
</tr>
<tr>
<td></td>
<td>MBD5</td>
<td>Methyl-CpG-binding domain protein 5</td>
</tr>
<tr>
<td></td>
<td>TCF4</td>
<td>Transcription factor 4</td>
</tr>
<tr>
<td></td>
<td>NRXN1</td>
<td>Neurexin-1</td>
</tr>
<tr>
<td></td>
<td>CNTNAP2</td>
<td>Contactin-associated protein-like 2</td>
</tr>
<tr>
<td>Mowat-Wilson syndrome</td>
<td>ZEB2</td>
<td>Zinc finger E-box-binding homeobox 2</td>
</tr>
<tr>
<td>Creatine deficiency syndromes</td>
<td>GAMT</td>
<td>Guanidinoacetate N-methyltransferase</td>
</tr>
<tr>
<td></td>
<td>GATM</td>
<td>Glycine amidinotransferase, mitochondrial</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis (NCL)</td>
<td>PPT1 (CLN1)</td>
<td>Palmitoyl-protein thioesterase 1</td>
</tr>
<tr>
<td></td>
<td>TPP1 (CLN2)</td>
<td>Tripeptidyl-peptidase 1</td>
</tr>
<tr>
<td></td>
<td>CLN3</td>
<td>Battenin</td>
</tr>
<tr>
<td></td>
<td>CLN5</td>
<td>Cereoid-lipofuscinosis neuronal protein 5</td>
</tr>
<tr>
<td></td>
<td>CLN6</td>
<td>Cereoid-lipofuscinosis neuronal protein 6</td>
</tr>
<tr>
<td></td>
<td>MFSBD8 (CLN7)</td>
<td>Major facilitator superfamily domain-containing protein 8</td>
</tr>
<tr>
<td></td>
<td>CLN8</td>
<td>Cereoid-lipofuscinosis neuronal protein 8</td>
</tr>
<tr>
<td></td>
<td>CTSB (CLN10)</td>
<td>Cathepsin D</td>
</tr>
<tr>
<td></td>
<td>KCTD7 (CLN14)</td>
<td>BTB/POZ domain-containing protein KCTD7</td>
</tr>
<tr>
<td>Adenosuccinate lyase deficiency</td>
<td>ADSL</td>
<td>Adenylosuccinate lyase</td>
</tr>
<tr>
<td>Cerebral folate deficiency</td>
<td>FOLR1</td>
<td>Folate receptor alpha</td>
</tr>
<tr>
<td>Epilepsy with variable learning and</td>
<td>GRIN2A</td>
<td>Glutamate receptor ionotropic, N-methyl-D-aspartate (NMDA) 2A Synapsin-1</td>
</tr>
<tr>
<td>behavioral disorders</td>
<td>SYN1</td>
<td></td>
</tr>
<tr>
<td>17q21.31 microdeletion syndrome</td>
<td>KANSL1</td>
<td>KAT8 regulatory nonspecific lethal (NSL) complex subunit 1</td>
</tr>
<tr>
<td>Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)</td>
<td>PNKP</td>
<td>Bifunctional polynucleotide phosphatase/kinase</td>
</tr>
</tbody>
</table>

*Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing.

### Table 593-5: Childhood Epileptic Syndromes with Generally Good Prognosis

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign neonatal familial convulsions</td>
<td>Febrile or afebrile seizures (benign) occur later in a minority</td>
</tr>
<tr>
<td>Infantile familial convulsions</td>
<td>Dominate; seizures often in clusters</td>
</tr>
<tr>
<td>Febrile convulsions plus syndromes (see Table 593-2)</td>
<td>Febrile and afebrile generalized convulsions, absence and myoclonic seizures occur in different members. Seizures usually generalized (GEFS+) but in some families may be focal</td>
</tr>
<tr>
<td>Benign myoclonic epilepsy of infancy</td>
<td>Often seizures during sleep; 1 rare variety with reflex myoclonic seizures (touch, noise)</td>
</tr>
<tr>
<td>Partial idiopathic epilepsy with rolandic spikes (benign epilepsy with centrotemporal spikes)</td>
<td>Seizures with falling asleep or on awakening; focal sharp waves with centrotemporal location on EEG</td>
</tr>
<tr>
<td>Idiopathic occipital partial epilepsy</td>
<td>Early childhood form with seizures during sleep and ictal vomiting; can occur as status epilepticus; later form with occipital spikes that block on eye opening; migrainous symptoms and seizures; not always benign</td>
</tr>
<tr>
<td>Petit mal absence epilepsy</td>
<td>Cases with absences only; some have generalized seizures; In most cases, absences disappear on therapy but there are resistant cases (unpredictable); 60-80% full remission</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Adolescence onset, with early morning myoclonic seizures and generalized seizures during sleep or upon awakening; often history of absences in childhood</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; GEFS+, generalized epilepsy with febrile seizures plus.

lesion or the result of a genetic, idiopathic, epilepsy. Focal seizures in a neonate may be seen because of focal lesions like perinatal stroke or because of a metabolic abnormality like hypocalcemia caused by immaturity of the brain connections. Focal and generalized motor seizures may be tonic–clonic, tonic, clonic, myoclonic, or atonic. Tonic seizures are characterized by increased tone or rigidity, and atonic seizures are characterized by flaccidity or lack of movement during a convulsion. Clonic seizures consist of rhythmic fast muscle contractions and slightly longer relaxations; myoclonus is a “shock-like” contraction of a muscle of <50 msec that is often repeated. The duration of the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an aura preceded the convulsion and the behavior of the child immediately preceding the seizure. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (particularly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted.

In addition to the assessment of cardiorespiratory and metabolic status, examination of a child with a seizure disorder should be geared toward the search for an organic cause. The child’s head circumference, cranial sutures, mental status, examination of a child with a seizure disorder should be geared toward the search for an organic cause. The child’s head circumference, cranial sutures, mental status, examination of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (particularly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted.

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Localizing neurologic signs, such as a subtle hemiparesis with hyperreflexia, an equivocal Babinski sign, and a downward-drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thymus, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

After the initial acute investigation, which often includes metabolic and CT scanning, depending on the clinical presentation in emergency room, in a child with a first nonfebrile seizure, it is recommended to obtain an EEG to help predict the risk of seizure recurrence. Subsequent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic or psychiatric examination, a seizure of focal onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children younger than 1 year of age. Other laboratory tests or lumbar punctures may be pursued depending on the specific clinical settings. Further details regarding the approach to a first seizure are included in Chapter 593.2.

### 593.1 Febrile Seizures

*Mohamad A. Mikati and Abeer J. Hani*

Febrile seizures are seizures that occur between the age of 6 and 60 mo with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A simple febrile seizure is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period. A complex febrile seizure is more prolonged (>15 min), is focal, and/or reoccurs within 24 hr. Febrile status epilepticus is a febrile seizure lasting longer than 30 min. Some use the term simple febrile seizure plus for those with recurrent febrile seizures within 24 hr. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure.

Between 2% and 5% of neurologically healthy infants and children experience at least 1, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are, understandably, concerning to the parents when they first witness them. Complex febrile seizures may have an approximately 2-fold long-term increase in mortality, as compared to the general population, over the subsequent 2 yr, probably secondary to coexisting pathology. There are no long-term adverse effects of having 1 or more simple febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% of infants younger than 1 yr old at febrile seizure onset. Several factors affect recurrence risk (Table 593-6). Although approximately 15% of children with epilepsy have had febrile seizures, only 2-7% of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures (Table 593-7).

#### GENETIC FACTORS

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant
trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and the genes predisposing to it remain to be identified. Identified single genes include FEB1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 genes on chromosomes 8q13–q21, 19p13.3, 2q24, 5q14–q15, 6q22–24, 18p11.2, 21q22, 5q34, 3p24.2-p23, and 3q26.2–q26.33. Only the function of FEB2 is known: it is a sodium channel gene, SCN1A.

Almost any type of epilepsy can be preceded by febrile seizures, and a few epilepsy syndromes typically start with febrile seizures. These are called febrile seizure plus (FSP) or, more accurately, febrile seizures that continue to occur after the temperature has normalized or for whom immunization status is unknown. "Meningitis should be considered in the differential diagnosis, and an EEG should be considered in evaluating the patient with febrile seizures."

**GEFS+** is an autosomal dominant syndrome with a highly variable phenotype. Onset usually occurs in early childhood and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic–clonic, absence, myoclonic, tonic, or myoclonic astatic seizures with variable degrees of severity. A febrile seizure plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

**Dravet syndrome** is the most severe of the phenotypic spectrum of febrile seizure-associated epilepsies. It constitutes a distinct entity in the onset of which is in infancy. Its onset is characterized by febrile and afebrile unilateral clonic seizures recurring every 1 or 2 mo. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, are more frequent, are focal and come in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the 2nd yr of life, myoclonus, atypical absence, and partial seizures occur frequently and developmentally delayed usually follows. This syndrome is usually caused by a de novo mutation, although rarely it is inherited in an autosomal dominant manner. The mutated gene is located on 2q24–31 and encodes for SCN1A, the same gene mutated in GEFS+ spectrum. However, in Dravet syndrome the mutations lead to loss of function and thus to a more severe phenotype. There are several milder variants of Dravet syndrome that manifest some but not all of the above features and that are referred to as Dravet syndrome spectrum or Borderland. Mutations in other genes may also cause Dravet syndrome or GEFS+ phenotypes.

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from vaccine encephalopathy (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome mutations, indicating that their disease is caused by the mutation and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed vaccine encephalopathy.

**EVALUATION**

Figure 593-1 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media, roseola and human herpesvirus (HHV) 6 infection, shigellosis, or similar infections, making the evaluation more demanding. In patients with febrile status, HHV-6B (more frequently) and HHV-7 infections were found to account for one-third of the cases. Several laboratory studies need to be considered in evaluating the patient with febrile seizures.

**Lumbar Puncture**

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 mo of age who present with fever and seizure, or if the child is ill-appearing or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6–12 mo of age who is deficient in *Haemophilus influenzae type b* and *Streptococcus pneumoniae* immunizations or for whom immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. In patients presenting with febrile status epilepticus in the absence of a central nervous system infection, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in the CSF) and the CSF protein and glucose are usually normal.

**Electroencephalogram**

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not normally be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 yr, and these do not predict later epilepsy. EEGs performed within 2 wk of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus, in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 wk have passed. An EEG should, therefore, generally be restricted to special cases in which epilepsy is highly suspected, and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 min in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, then an EEG can help distinguish between ongoing seizure activity and a prolonged postictal period, sometimes termed a nonepileptic twilight state. EEG can also be helpful in patients who present with febrile status epilepticus because the presence of focal slowing present on the EEG obtained within 72 hr of the status has been shown to be highly associated with MRI evidence of acute hippocampal injury.

**Blood Studies**

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and complete blood count) are not routinely recommended in the work-up of a child with a first simple febrile seizure. Blood glucose should be determined in children with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in abnormalities of the physical examination. If clinically indicated (e.g., in a history or physical examination...
Neuroimaging
A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The work-up of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 11% of children with febrile status epilepticus are reported to have (usually) unilateral swelling of their hippocampus acutely, which is followed by subsequent long-term hippocampal atrophy. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

TREATMENT
In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with 1 or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 min, acute treatment with diazepam, lorazepam, or midazolam is needed (see Chapter 593.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to be given at the time of reoccurrence of a febrile seizure lasting longer than 5 min (see Table 593.12 for dosing). Alternatively, buccal or intranasal midazolam may be used and is often preferred by parents. Intravenous benzodiazepines, phenobarbital, phenytoin, or valproate may be needed in the case of febrile status epilepticus. If the parents are very anxious concerning their child’s seizures, intermittent oral diazepam (0.33 mg/kg every 8 hr during fever) or intermittent rectal diazepam (0.5 mg/kg administered as a rectal suppository every 8 hr), can be given during febrile illnesses. Intermittent oral nitrazepam, clobazam, and clonazepam (0.1 mg/kg/day) have also been used. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Other therapies have included continuous phenobarbital (4-5 mg/kg/day in 1 or 2 divided doses), and continuous valproate (20-30 mg/kg/day in 2 or 3 divided doses). In the vast majority of cases, it is not justified to use continuous therapy owing to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure, probably because the seizure often occurs as the temperature is rising or falling. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. Currently available data indicate that the possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appears appropriate.

Bibliography is available at Expert Consult.

593.2 Unprovoked Seizures
Mohamad A. Mikati and Abeer J. Hani

HISTORY AND EXAMINATION
Acute evaluation of a first seizure includes assessment of vital signs and respiratory and cardiac function, and institution of measures to normalize and stabilize them as needed. Signs of head trauma, abuse, drug intoxication, poisoning, meningitis, sepsis, focal abnormalities, increased intracranial pressure, herniation, neurocortaneous stigmata, brainstem dysfunction, and/or focal weakness should all be sought because they could suggest an underlying etiology for the seizure.

The history should also include details of the seizure manifestations, particularly those that occurred at its initial onset. These could give clues to the type and brain localization of the seizure. One should also probe for previous signs or symptoms of other seizures in the preceding weeks, or longer, that the parents may have overlooked and did not report. In some instances, if the events have been going on for a time and there is a question about their nature (e.g., sleep myoclonus vs seizures), then the family could video record the patient and make the video available to the healthcare provider. Having the parents imitate the seizure can also be helpful. Seizure patterns (e.g., clustering), precipitating conditions (e.g., sleep or sleep deprivation, television, visual patterns, mental activity; stress), exacerbating conditions (e.g., menstrual cycle, medications), frequency, duration, time of occurrence, and other characteristics need to be carefully documented (see Chapter 593.9). Parents often overlook, do not report, or underreport absence, complex partial, or myoclonic seizures. A history of personality change or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. Certain medications such as stimulants or antihistamines, particularly sedating ones, can precipitate seizures. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Details of the spells can suggest nonepileptic paroxysmal disorders that mimic seizures (see Chapter 594).

DIFFERENTIAL DIAGNOSIS
This involves consideration of nonepileptic paroxysmal events (see Chapter 594), determination of the seizure type, as classified by the new ILAE system (see Table 593-1) and consideration of potential underlying etiologies. Some seizures might begin with auras, which are sensory experiences reported by the patient and not observed externally. These can take the form of visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending upon the precise localization of the origin of the seizures.

Motor seizures can be tonic (sustained contraction), clonic (rhythmic contractions), myoclonic (rapid shock-like contractions, usually <50 msec in duration, that may be isolated or may repeat but usually are not rhythmic), atomic, or astatic. Astatic seizures often follow myoclonic seizures and cause a very momentary loss of tone with a sudden fall. Atomic seizures, on the other hand, are usually longer and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atomic, or astatic seizures based on the history alone when the family reports only that the patient “falls”; in such cases, the seizure may be described as a drop attack. Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a head drop. Tonic, clonic, myoclonic, and atomic seizures can be focal (including 1 limb or 1 side only), focal with secondary generalization, or primary generalized. Epileptic spasms (axial spasms, these terms being preferred over infantile spasms because they can occur beyond infancy) consist of flexion or extension of truncal and extremity musculature that is sustained for 1-2 sec, shorter than what is seen in tonic seizures, which last longer than 2 sec. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed epilepsy partialis continua.

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for few seconds. Typical absences are associated with 3 Hz spike–and–slow-wave discharges and with petit mal epilepsy, which has a good prognosis. Atypical absences are associated with 1-2 Hz spike–and–slow-wave discharges, and with head atonia and myoclonus during the seizures. They occur in Lennox–Gastaut syndrome, which has a poor prognosis. Juvenile absences are similar to typical absences but are associated with 4-5 Hz spike-and-slow waves and occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of epilepsy syndrome with which a particular patient is afflicted (Table 593-8; see Chapter 593.3 and 593.4).

Family history of certain forms of epilepsy, like benign neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Head circumference can indicate
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Bibliography


Grill MF, Ng YT: "Simple febrile seizures plus (SFS +)": more than one febrile seizure within 24 hours is usually okay, *Epilepsy Behav* 27:472–475, 2013.


the presence of microcephaly or of macrocephaly. Eye exam may show optic disc edema, retinal hemorrhages, chorioterinitis, colobomata (associated with brain malformations), a cherry-red spot, optic atrophy, macular changes (associated with genetic neurodegenerative and storage diseases), or phakomas (associated with tuberous sclerosis). Skin exam could show a trigeminal V1 distribution capillary hemangioma (associated with Sturge-Weber syndrome), hypopigmented lesions (sometimes associated with tuberous sclerosis and detected more reliably by viewing the skin under UV light), or other neurocutaneous manifestations such as Shagreen patches and adenoma sebaceum (associated with tuberous sclerosis), or whorl-like hypopigmented areas (hypomelanosis of Ito, associated with hemimegalencephaly). Subtle asymmetries on the exam such as drift of 1 of the extended arms, posturing of an arm on stress gait, slowness in rapid alternating movements, small hand or thumb and thumb nail on 1 side, or difficulty in hopping on 1 leg relative to the other can signify a subtle hemiparesis associated with a lesion on the contralateral side of the brain.

Guidelines on the evaluation of a first unprovoked nonfebrile seizure include a careful history and physical examination and brain imaging by head CT or MRI. Emergency head CT in the child presenting with a first unprovoked nonfebrile seizure is often useful for acute management of the patient. Laboratory studies are recommended in specific clinical situations: Spinal tap is considered in patients with suspected meningitis or encephalitis, in children without brain swelling or papilledema, and in children in whom a history of intracranial bleeding is suspected without evidence of such on head CT. In the second of these, examination of the CSF for xanthochromia is essential. Electrocardiography (ECG) to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see Chapter 594). EEG is highly recommended to assess for focal abnormalities and predict seizure recurrence.

**LONG-TERM APPROACH TO THE PATIENT AND ADDITIONAL TESTING**

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in Table 593-9. This emphasizes the total approach to the patient, including identification, if possible, of the underlying etiology of the epilepsy and the impairments that result from it. The impairments are very often just as important as, if not more important than, the seizures themselves. Most epilepsy syndromes are potentially caused by any 1 of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see Table 593-2). Different mutations of the same gene can result in different epilepsy syndromes, and mutations of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy has been limited to patients manifesting specific underlying malformational, metabolic, or degenerative disorders, patients with severe named epilepsy syndromes (such as West and Dravet syndromes and progressive

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**Table 593-8**

<table>
<thead>
<tr>
<th>Selected Epilepsy Syndromes by Age of Onset</th>
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<tbody>
<tr>
<td>NEONATAL PERIOD</td>
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<tr>
<td>Benign familial neonatal seizures (BFNS)</td>
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<tr>
<td>Early myoclonic encephalopathy (EME)</td>
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<tr>
<td>Ohtahara syndrome</td>
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<tr>
<td>INFANCY</td>
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<tr>
<td>Epilepsy of infancy with migrating focal seizures</td>
</tr>
<tr>
<td>West syndrome</td>
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<tr>
<td>Myoclonic epilepsy in infancy (MEI)</td>
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<tr>
<td>Benign infantile seizures</td>
</tr>
<tr>
<td>Benign familial infantile epilepsy</td>
</tr>
<tr>
<td>Dravet syndrome</td>
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<tr>
<td>Myoclonic encephalopathy in nonprogressive disorders</td>
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<tr>
<td>CHILDHOOD</td>
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<tr>
<td>Febrile seizures plus (FS+) (can start in infancy; this can be generalised [GEFS+] or with focal seizures)</td>
</tr>
<tr>
<td>Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)</td>
</tr>
<tr>
<td>Epilepsy with myoclonic atonic (previously astatic) seizures</td>
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<tr>
<td>Benign epilepsy with centrotemporal spikes (BCECTS)</td>
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<tr>
<td>Late-onset childhood occipital epilepsy (Gastaut type)</td>
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<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE)</td>
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<tr>
<td>Epilepsy with myoclonic absences</td>
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<tr>
<td>Lennox-Gastaut syndrome</td>
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<tr>
<td>Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
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<tr>
<td>Childhood absence epilepsy (CAE)</td>
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<tr>
<td>ADOLESCENCE–ADULT</td>
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<tr>
<td>Juvenile absence epilepsy (JAE)</td>
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<tr>
<td>Juvenile myoclonic epilepsy (JME)</td>
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<tr>
<td>Epilepsy with generalized tonic–clonic seizures alone</td>
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<tr>
<td>Progressive myoclonus epilepsies (PME)</td>
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<tr>
<td>Autosomal dominant epilepsy with auditory features (ADEAF)</td>
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<tr>
<td>Other familial temporal lobe epilepsies</td>
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<tr>
<td>AGE-RELATED (AGE OF ONSET LESS SPECIFIC)</td>
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<tr>
<td>Familial focal epilepsy with variable foci (childhood to adult)</td>
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<tr>
<td>Reflex epilepsies</td>
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<tr>
<td>SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY</td>
</tr>
<tr>
<td>Benign neonatal seizures (BNS)</td>
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<tr>
<td>Febrile seizures (FS)</td>
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<tr>
<td>EPILEPTIC ENCEPHALopathies</td>
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<tr>
<td>EME</td>
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<tr>
<td>Ohtahara syndrome</td>
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<tr>
<td>Migrating partial seizures of infancy</td>
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<tr>
<td>West syndrome</td>
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<tr>
<td>Dravet syndrome</td>
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<tr>
<td>Myoclonic encephalopathy in nonprogressive disorders</td>
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<tr>
<td>Epilepsy with myoclonic astatic seizures</td>
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<tr>
<td>Lennox-Gastaut syndrome</td>
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<tr>
<td>Epileptic encephalopathy with CSWS</td>
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<tr>
<td>Landau-Kleffner syndrome</td>
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<tr>
<td>OTHER SECONDARY GENERALIZED EPILEPSIES</td>
</tr>
<tr>
<td>Generalized epilepsy secondary to neurodegenerative disease</td>
</tr>
<tr>
<td>Progressive myoclonus epilepsies</td>
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</tbody>
</table>

**Table 593-9**

<table>
<thead>
<tr>
<th>Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy</th>
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<tbody>
<tr>
<td>Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that uses standardized terminology and that is sufficiently flexible to take into account the practical and dynamic aspects of epilepsy diagnosis:</td>
</tr>
<tr>
<td>- Axis 1: Ictal phenomenology, used to describe ictal events with any degree of detail needed.</td>
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<tr>
<td>- Axis 2: Seizure type, from the List of types of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.</td>
</tr>
<tr>
<td>- Axis 3: Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.</td>
</tr>
<tr>
<td>- Axis 4: Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.</td>
</tr>
<tr>
<td>- Axis 5: Impairment; this is often useful to make sure one does not overlook the consequences of epilepsy, such as medication side effects, and learning and socialization difficulties.</td>
</tr>
</tbody>
</table>


Patients with recurrent seizures, specifically with 2 seizures spaced apart by longer than 24 hr, warrant further work-up directed at the underlying etiology. In patients with drug-resistant epilepsy, or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic work-up, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very-long-chain fatty acids, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).
3. Serum immune isoelectric focusing is performed for carbohydrate-deficient transferrin.
4. CSF glucose testing looks for glucose transporter deficiency, and CSF can be examined for cells and proteins (for para-infectious and postinfectious syndromes, and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).
5. Other laboratory studies include immunoglobulin (Ig) G index, NMDA (N-methyl-D-aspartate) receptor antibodies, and measles titers.
6. CSF tests can also confirm with, the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies. In infants who do not respond immediately to antiepileptic therapy, vitamin B₆ (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a predAnnotationination baseline recording period. Prior to the vitamin B₆ trial, a pipicolic acid level and urine and CSF α-aminoadipic acid semialdehyde levels should be drawn, because they often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Also patients with cerebral folate deficiency can have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg) and folinic acid (up to 3 mg/kg) over several weeks can help diagnose these rare disorders while waiting for the definitive diagnosis from CSF or genetic testing for these disorders. Certain EEG changes such as continuous spike–and–slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.
7. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy is performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.
8. Gene testing looks for specific disorders that can manifest with seizures, including SCN1A mutations in Dravet syndrome; ARX gene for West syndrome in boys; MECP2, CDKL5, and protocadherin 19 for Rett syndrome and similar presentations; syntaxin binding protein for Ohtahara syndrome; and polymersase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.
9. Muscle biopsy can be performed for mitochondrial enzymes and coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease is sometimes needed.
10. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole-exome sequencing is also available. These can be helpful in selected patients.

Partial (now referred to as focal) seizures account for approximately 40% of seizures in children and can be divided into simple partial seizures (currently referred to in the most recent ILAE classification as focal seizures without impairment of consciousness), in which consciousness is not impaired, and complex partial seizures (currently referred to as focal seizures with impairment of consciousness, also called focal dyscognitive seizures), in which consciousness is affected. Simple and complex partial seizures can each occur in isolation, one can temporarily lead to the other (usually simple to complex), and/or each can progress into secondary generalized seizures (tonic, clonic, atonic, or most often tonic–clonic).

Focal Seizures Without Impairment of Consciousness

These can take the form of sensory seizures (auras) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (jacksonian) march from face to arm to leg, adveresive head and eye movements to the contralateral side, or postictal (Todd) paralysis that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and less likely than tics to manifest different types in a given patient.

Focal Seizures With Impairment of Consciousness

These seizures usually last 1-2 min and are often preceded by an aura, such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 yr old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. Automatisms are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night, too. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.
Bibliography


SECONDARY GENERALIZED SEIZURES

Seizures of this type were previously known as focal seizures with impairment of consciousness evolving to bilateral convulsive seizures. Secondary generalized seizures can start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus), or as simple or complex partial seizures with subsequent clinical generalization. There is often adverse eye and head deviation to the side contralateral to the side of the seizure focus followed by generalized tonic, clonic, or tonic–clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 min. Tonic focal or secondary generalized seizures often manifest adverse head deviation to the contralateral side, or fencing, hemi- or full figure-of-four arm, or Statue of Liberty postures. These postures often suggest frontal origin, particularly when consciousness is preserved during them, indicating that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A sleep-deprived EEG with recording during sleep increases the diagnostic yield and is advisable in all patients whenever possible (Fig. 593-2). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, then longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hr video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough, because it then can allow visualization of the clinical events and the corresponding EEG tracing.

Brain imaging is critical in patients with focal seizures. In general, MRI is preferable to CT, which misses subtle but occasionally potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 593-3).

BENIGN EPILEPSY SYNDROMES WITH FOCAL SEIZURES

The most common such syndrome is benign childhood epilepsy with centrotemporal spikes which typically starts during childhood (ages 3-10 yr) and is outgrown in adolescence. The child typically wakes up at night owing to a focal (simple partial) seizure causing buccal and throat tingling and tonic or clonic contractions of 1 side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Dyscognitive focal (complex partial) and secondary generalized seizures can also occur. EEG shows typical broad-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to antiepileptic drugs (AEDs) such as carbamazepine. In some patients who only have rare and mild seizures treatment might not be needed.

Benign epilepsy with occipital spikes can occur in early childhood (Panayiotopoulos type) and manifests with complex partial seizures with icctal vomiting, or they appear in later childhood (Gastaut type) with complex partial seizures, visual auras, and migraine headaches. Both are typically outgrown in a few years. Manifestations may include visual hallucinations and postictal headache (epilepsy–migraine sequence).

In infants, several less-common benign infantile familial convulsion syndromes have been reported. For some of these, the corresponding gene mutation and its function are known (see Tables 593-2 and 593-5), but for others, the genetic underpinnings are yet to be determined. Specific syndromes include benign infantile familial convulsions with parietooccipital foci linked to chromosomal loci 19q and 2q, benign familial infantile convulsions with associated choreoathetosis linked to chromosomal locus 16p12-q12, and benign

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**Figure 593-2 A**, Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe (arrow) in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes (arrow) characteristic of benign partial epilepsy with centrotemporal spikes. **B**, Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypersomnia with an irregular multifocal high-voltage spike and wave activity with chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.
infantile familial convulsions with hemiplegic migraine linked to chromosome 1. A number of benign infantile nonfamilial syndromes have been reported, including dyscognitive focal (complex partial) seizures with temporal foci, secondary generalized tonic–clonic seizures with variable foci, tonic seizures with midline foci, and partial seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly, often necessitating only short-term (e.g., 6 mo), if any, therapy. Nocturnal autosomal dominant frontal lobe epilepsy has been linked to acetylcholine-receptor gene mutations and manifests with nocturnal seizures with dystonic posturing and agitation, screaming, kicking that respond promptly to carbamazepine. Several other less-frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults (see Table 593.2).

SEVERE EPILEPSY SYNDROMES WITH FOCAI SEIZURES

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than idiopathic genetic epilepsy. It is important to note that many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, drug-resistant epilepsy with focal seizures is often caused by severe metabolic problems, hypoxic–ischemic injury, or congenital malformations. In addition, in this age group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called migrating partial seizures of infancy has been described. In infants and older children, several types of lesions, which can occur in any lobe, can cause intractable epilepsy and seizures and some cases may be secondary to mutations in the calcium-sensitive potassium channel KCNT1. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber hemangioma, tuberous sclerosis, and congenital tumors such as ganglioglioma, and dysembryoplastic neuroepithelial tumors, as well as others. The intractable seizures can be simple partial, complex partial, secondary generalized, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut and has been termed by some pseudo–Lennox-Gastaut syndrome.

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is mesial (also termed medial) temporal sclerosis, a condition often preceded by febrile seizures and, rarely, genetic in origin. Pathologically, these patients have atrophy and gliosis of the hippocampus and, in some, of the amygdala. It is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other symptomatic or cryptogenic partial or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia (Landau-Kleffner epileptic aphasia syndrome). Activation of frontal and secondary generalized discharges in sleep leads to more global delay secondary to the syndrome of continuous spike waves in slow-wave sleep (>85% of slow-wave sleep recording dominated by discharges).

The syndrome of Rasmussen encephalitis is a form of chronic encephalitis that manifests with unilateral intractable partial seizures, epilepsy partialis continua, and progressive hemiparesis of the affected side, with progressive atrophy of the contralateral hemisphere. The etiology is usually unknown. Some cases have been attributed to cytomegalovirus and others to anti-NMDA receptor autoantibodies.

593.4 Generalized Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Abeer J. Hani

ABSENCE SEIZURES

Typical absence seizures usually start at 5–8 yr of age and are often, owing to their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike complex partial seizures they do not have an aura, usually last for only a few seconds, and are accompanied by eye lid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms of complex partial seizures (absence seizures can have simple automatisms like lip-smacking or picking at clothing and the head can minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3–5 min can precipitate the seizures and the accompanying 3 Hz spike–and–slow-wave
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discharges. The presence of periorbital, lid, perioral, or limb myoclonic jerks with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early onset absence seizures (before the age of 4 yr) should trigger evaluation for glucose transporter defect that is often associated with low CSF glucose levels and an abnormal sequencing test of the transporter gene.

Atypical absence seizures have associated myoclonic components and tonic changes of the head (head drop) and body and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1-2 Hz spike-and-slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4-6 Hz spike-and-slow-wave and polyspike-and-slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see “Benign Generalized Epilepsies”).

**GENERALIZED MOTOR SEIZURE**

The most common generalized motor seizures are generalized tonic-clonic seizures that can be either primarily generalized (bilateral) or secondarily generalized (as described in Chapter 593.3) from a unilateral focus. If there is no partial component, then the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops usually 1-2 min later. Incontinence and a postictal period often follow. The latter usually lasts for 30 min to several hours with semicoma or obtundation and postictal sleepiness, weakness, ataxia, hyper- or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if possible, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner’s finger). Many patients have single idiopathic generalized tonic-clonic seizures that may be associated with intercurrent illness or with a cause that cannot be ascertained (see Chapter 593.2). Generalized tonic, atonic, and astatic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see “Benign Generalized Epilepsies” and “Severe Generalized Epilepsies”).

**BENIGN GENERALIZED EPILEPSIES**

Petit mal epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic-clonic seizures, half before and half after the onset of absences. Benign myoclonic epilepsy of infancy consists of the onset of myoclonic and other seizures during the 1st yr of life, with generalized 3 Hz spike-and-slow-wave discharges. Often, it is initially difficult to distinguish this type from more-severe syndromes, but follow-up clarifies the diagnosis. Febrile seizures plus syndrome manifests febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see Chapter 593.1).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to mutations in many genes including CACNB4; CLNC2; EJM2, 3, 4, 5, 6, 7, 9; GABRA1; GABRD; and Myoclonil1/EFHC1 (see Table 593-2). Typically, it starts in early adolescence with 1 or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic-clonic or clonic-tonic-clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation, or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4-5 Hz polyspike-and-slow-wave discharges. There are other forms of generalized epilepsies such as photoparoxysmal epilepsy, in which generalized tonic-clonic, absence or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels and viewing video games. Other forms of reflex (i.e., stimulus-provoked) epilepsy can occur; associated seizures are usually generalized, although some may be focal (see Table 593-1 and Chapter 593.9).

**SEVERE GENERALIZED EPILEPSIES**

Severe generalized epilepsies are associated with intractable seizures and developmental delay. Early myoclonic infantile encephalopathy starts during the 1st 2 mo of life with severe myoclonic seizures and burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as nonketotic hyperglycinemia. Early infantile epileptic encephalopathy (Ohtahara syndrome) has similar age of onset and EEG but manifests tonic seizures and is usually caused by brain malformations or syntaxin binding protein 1 mutations. Severe myoclonic epilepsy of infancy (Dravet syndrome) starts as focal febrile status epilepticus or focal febrile seizures and later manifests myoclonic and other seizure types (see Chapter 593.1).

West syndrome starts between the ages of 2 and 12 mo and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called hypsarrhythmia (see Fig. 593-2). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with cryptogenic (sometimes called idiopathic, now referred to as unknown etiology) West syndrome have normal development before onset, while patients with symptomatic West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, or other etiologies (see Chapter 593.2). In boys, West syndrome can also be caused by ARX gene mutations (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases of unknown etiology (cryptogenic cases, i.e., cases that are not symptomatic of metabolic or structural brain disorder), is a medical emergency because diagnosis delayed for 3 wk or longer can affect long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or for other benign paroxysmal syndromes (see Chapter 594).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 yr and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, myoclonic, atonic, and tonic seizures. The tonic seizures occur either in wakefulness (causing falls and injuries) or also, typically, in sleep. The third component is the EEG findings (see Fig. 593-2): 1-2 Hz spike-and-slow waves, polyspike bursts in sleep, and a slow background in wakefulness. Patients commonly have myoclonic, tonic, and other seizure types that are difficult to control, and most are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some, but not all, patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. Myoclonic atatic epilepsy is a syndrome similar to, but milder than, Lennox-Gastaut syndrome that usually does not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by tonic seizures causing head nodding as well as tonic, clonic and stimulus sensitive seizures is the nodding syndrome, which is a recently described epidemic type of epilepsy seen in some African countries and often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is unknown.

Progressive myoclonic epilepsies are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. Type I or Unverricht-Lundborg disease (secondary to a cystatin B mutation) is more slowly progressive than the other types and usually starts in adolescence. Type II or Lafora body disease can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the 2nd or 3rd decade. It can be associated with photosensitivity, manifests periodic acid-Schiff-positive Lafora inclusions on muscle or skin biopsy (in eccrine...
sweat gland cells), and has been shown to be caused by laforin (EPM2A) or malin (EPM2B) gene mutations. Other causes of progressive myoclonic epilepsy include myoclonic epilepsy with ragged red fibers, sialidosis type I, neuronal ceroid lipofuscinosis, juvenile neuropathic Gaucher disease, dentatorubral-pallidoluysian atrophy, and juvenile neuroaxonal dystrophy.

**Myoclonic encephalopathy in nonprogressive disorders** is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

**Landau-Kleffner syndrome** is a rare condition of unknown cause characterized by loss of language skills attributed to auditory agnosia in a previously normal child. At least 70% have associated clinical seizures, but some do not. The seizures when they occur are of several types, including focal, generalized tonic–clonic, atypical absence, partial complex, and, occasionally, myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non–rapid eye movement sleep; thus, a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep, particularly if the awake record is normal. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome with continuous spike waves in slow-wave sleep, the discharges are more likely to be frontal or generalized and the delays more likely to be global. The approach and therapy to the 2 syndromes are similar. Valproic acid is often the anticonvulsant that is used first to treat the clinical seizures and may help the aphasia. Some children respond to clonazepam, to the combination of valproic acid and cllobazam, or to levetiracetam. For therapy of the aphasia, nocturnal diazepam therapy (0.2-0.5 mg/kg PO at bedtime for several months) is often used as first- or second-line therapy, as are oral steroids. Oral prednisone is started at 2 mg/kg/24 hr for 1 mo and decreased to 1 mg/kg/24 hr for an additional month. With clinical improvement, the prednisone is reduced further to 0.5 mg/kg/24 hr for up to 6-12 mo. Long-term therapy is often needed irrespective of what the patient responds to. If the seizures and aphasia persist after diazepam and steroids trials, then a course of intravenous immunoglobulins should be considered. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

**Amenably treatable metabolic epilepsies** are becoming increasingly recognized. **Pyridoxine-dependent epilepsy** typically presents as neonatal encephalopathy shortly after birth with, at times, report of increased fetal movements (seizure) in utero. There are associated gastrointestional symptoms with emesis and abdominal distention, neurologic irritability, sleepless and facial grimacing along with recurrent partial motor seizure, generalized tonic seizures, and myoclonus. Seizures are usually refractory and may progress to status epilepticus if no pyridoxine is used. Some cases start in infancy or in childhood. Diagnosis is confirmed by the presence of elevated plasma, urine and CSF α-aminoacidic semialdehyde and elevated plasma and CSF pipercolic acid levels. The presence of either homozygous or compound heterozygous mutations in ALDH7A1 alleles (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (up to 600 mg/day) is started at 2 mg/kg/24 hr for 1 mo and decreased to 1 mg/kg/24 hr for an additional month. Clinical improvement, the prednisone is reduced further to 0.5 mg/kg/24 hr for up to 6-12 mo. Long-term therapy is often needed irrespective of what the patient responds to. If the seizures and aphasia persist after diazepam and steroids trials, then a course of intravenous immunoglobulins should be considered. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

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593.5 Mechanisms of Seizures
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One can distinguish in the pathophysiology of epilepsy 4 distinct, often sequential, mechanistic processes. First is the underlying etiology, which is any pathology or pathologic process that can disrupt neuronal function and connectivity and that eventually leads to the second process (epileptogenesis) which makes the brain epileptic. The underlying etiologies of epilepsy are diverse and include, among other entities, brain tumors and malformations, strokes, scarring, or mutations of specific genes. These mutations can involve voltage-gated channels (Na⁺, K⁺, Ca²⁺, Cl⁻, and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ-aminobutyric acid A receptors [GABAₐ]) or other proteins. In some but not in all such mutations, the molecular and cellular deficits caused by the mutations have been identified. For example, in Dravet syndrome, the loss of function mutation in the SCN1A gene causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. In many other epileptic conditions, a clear etiology is still lacking and in others the etiology may be known, but it is still not

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Cerebral folate deficiency, which also responds to high doses of folic acid (2-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinasias, and autism. CSF 5-methyltetrahydrofolate levels are decreased with normal plasma and red blood cell folate levels. There are usually mutations in the folate receptor (FOLR1) gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. Tetrahydrobiopterin deficiencies with or without hyperphenylalaninemia may present with epilepsies, and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes) and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. Creatine deficiency syndromes present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by abnormal levels of urine creatine and guanidinoacetic acid and/or, depending on the type of underlying genetic etiology, with absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions are helpful. Biotinidase deficiency presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and organic profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine use. Developmental delay, epilepsy, and neonatal diabetes is caused by activating mutations in the adenosine triphosphate-sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the central nervous system (CNS) symptoms and affect seizures. Hyperinsulinism-hyperammonemia syndrome is caused by activating mutations of the glutamate dehydrogenase encoded by the GLUD1 gene. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 μmol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). GLUT-1 deficiency syndrome classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain typically diagnosed by genetic testing or finding of low CSF lactate and CSF glucose, or low CSF to serum glucose ratios (less than 0.4). The manifestations of the disease are usually responsive to ketogenic diet.
known how the identified underlying genetic etiology or brain insult results in epileptogenesis.

Second, epileptogenesis is the mechanism through which the brain, or part of it, turns epileptic. The presence of this process explains why some patients with the above pathologies develop epilepsy and some do not. Kindling is an animal model for human focal epilepsy in which repeated electrical stimulation of selected areas of the brain with a low-intensity current initially causes no apparent changes but with repeated stimulation results in epilepsy. This repetitive stimulation can lead to temporal lobe epilepsy, for example, through activation of metabotropic and ionotropic glutamate receptors (by glutamate), as well as the tropomysin-related kinase B receptor (by brain-derived neurotrophic factor and neurotrophin-4). This leads to an increase in the intraneuronal calcium, which, in turn, activates calcium calmodulin–dependent protein kinase and calcineurin, a phosphatase, resulting eventually in calcium-dependent epileptogenic gene expression (e.g., c-fos) and promotion of mossy fiber sprouting. Mossy fibers are excitatory fibers that connect the granule cells to the CA3 region within the hippocampus, and their pathologic sprouting underlies increased excitability in medial temporal lobe epilepsy associated with mesial temporal sclerosis in humans and in animal models. The cell loss in the CA3 region that is a characteristic of mesial temporal sclerosis (presumably resulting from an original insult such as a prolonged febrile status epilepticus episode or hypoxia) leads to a pathologic attempt at compensation by sprouting of the excitatory mossy fibers. Consequently, mossy fiber sprouting, which has been demonstrated in humans also, leads to increased excitability and to epilepsy. Complex febrile seizures in rats induce hyperactivation of, paradoxically excitatory, GABAergic interneurons leading to granule cell ectopia and to subsequent temporal lobe epilepsy. Possibly similar yet to be fully characterized epileptogenesis mechanisms may underlie other focal epilepsies.

Later, the role of large-scale molecular cell signaling pathways in epileptogenesis, namely the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)-silencing transcription factor (REST; also known as neuron-restrictive silencer factor) pathways have been implicated in the mechanisms leading to epilepsy. The mTOR pathway in tuberous sclerosis, hemimegalencephaly and cortical dysplasia–related epilepsies, Ras/ERK in a number of syndromes, and REST in epileptogenesis after acute neuronal injury.

The third process is the resultant epileptic state of increased excitability that is present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. In a seizure focus, each neuron has a stereotypic synchronized response called paroxysmal depolarization shift that consists of a sudden depolarization phase, resulting from glutamate and calcium channel activation, with a series of action potentials at its peak followed by an after-hyperpolarization phase, resulting from activation of potassium channels and GABA receptors that open chloride channels. When the after-hyperpolarization is disrupted in a sufficient number of neurons, the inhibitory surround is lost and a population of neurons fire at the same rate and time, resulting in a seizure focus. In childhood absence epilepsy, the discharging neurons also develop a paroxysmal depolarization shift similar to the one found in partial epilepsy. However, the mechanism of paroxysmal depolarization shift generation is different because it involves thalamocortical connections bilaterally. T-type calcium channels on thalamic relay neurons are activated during hyperpolarization by GABAergic interneurons in the reticular thalamic nucleus, which results in enhancement of synchronization in the thalamocortical loop and consequently in the typical generalized spike-wave pattern. In tumor-related epilepsy, particularly in that related to oligodendroglioma, the voltage-gated sodium channels are present on the surface of tumor cells at a higher density than on normal cells, and their inactivation is impaired by the alkaline pH present in this condition. In hypothalamic hamartoma causing gelastic seizures, clusters of GABAergic interneurons spontaneously fire, thus synchronizing the output of the hypothalamic hamartoma neurons projecting to the hippocampus.

The fourth process is seizure-related neuronal injury as demonstrated by MRI in patients after prolonged febrile and afebrile status epileptics. Many such patients show acute swelling in the hippocampus and long-term hippocampal atrophy with sclerosis on MRI. Nonetheless in most patients with seizure-related MRI abnormalities, the findings are transient. In experimental models, the mechanisms of such injuries have been shown to involve both apoptosis and necrosis of neurons in the involved regions. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of intractable epilepsy.

In infantile spasms, recently developed animal models suggest that increases in stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms. Prior positron emission tomography data suggest that an interaction between focal cortical lesions and the brainstem raphe nuclei is important at least in some infantile spasm patients.

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593.6 Treatment of Seizures and Epilepsy

Mohamad A. Mikati and Abeer J. Hani

DECIDING ON LONG-TERM THERAPY

After a first seizure, if the risk of recurrence is low, such as when the patient has normal neurodevelopmental status, EEG, and MRI (risk approximately 20%), then treatment is usually not started. If the patient has abnormal EEG, MRI, development, and/or neurologic exam, and/or a positive family history of epilepsy, then the risk is higher and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents’ ability to deal with recurrences or AED drug therapy in children. The decision is therefore always individualized. All aspects of this decision-making process should be discussed with the family. Figure 593-4 presents an overview of the approach to the treatment of seizures and epilepsy.

COUNSELING

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to deal with them. It is important to establish a successful therapeutic alliance. Restrictions on driving (in adolescents) and on swimming are usually necessary (Table 593-10). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the responsibility of the patient. The physician then is requested to complete a specific form for patients who are being cleared to drive. Also in most states, a seizure-free period of 6 mo, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or sea, and underwater diving are prohibited, but swimming in swimming pools may be allowable. When swimming, even patients with epilepsy that is under excellent control should be under the continuous supervision of an observer who is aware of their condition and capable of lifeguard-level rescue.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. Any activity where a seizure might cause a dangerous fall should be avoided; these activities include rope climbing, use of the parallel bars, and high diving. Participation in collision or contact sports depends on the patient’s condition. Epileptic children should not automatically be banned from participating in hockey, baseball, basketball, football, or wrestling. Rather, individual consideration should be based on the child’s specific case (see Table 593-10).

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, psychologic evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with the epilepsy. Epilepsy does carry a risk of increased
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mortality (2 or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying the epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies, or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus, family members can usually be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are currently advertised seizure-detection equipment that use motion sensors placed under the mattress to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging in that they were useful in detecting a majority of generalized tonic–clonic seizures during sleep (see bibliography for details). Whether such measures can reduce sudden unexpected death in epilepsy (SUDEP) risk remains to be seen and the parents need to guard against being overprotective to avoid adversely affecting the psychology of the child. Education about what to do in case of seizures, the choices of treatment or no treatment and of medications and their side effects, and potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

**MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS**

AEDs reduce excitability by interfering with the sodium, potassium or calcium ion channels, by reducing excitatory neurotransmitter release...
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- Propionic acid/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam binds to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly results in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

CHOICE OF DRUG ACCORDING TO SEIZURE TYPE AND EPILEPSY SYNDROME

Drug therapy should be based on the type of seizure and the epilepsy syndrome as well as on other individual factors. In general, the drugs of first choice for focal seizures and epilepsies are oxcarbazepine and carbamazepine; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, valproate and lamotrigine; for Lennox-Gastaut syndrome, clobazam, valproate, topiramate, lamotrigine, and, most recently, as add on, rufinamide; and for infantile spasms, adrenocorticotropic hormone (ACTH). There is significant controversy about these choices, and therapy should always be individualized (see Choice of Drug: Other Considerations below and Table 593-10).

West syndrome is best treated with ACTH. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m² (divided into twice-daily intramuscular injections of 75 units/m², the lot number is recorded) administered over a 2-wk period with a subsequent gradual taper over a 2-wk period (30 units/m² in the morning or function, or by enhancing GABAergic inhibition (Fig. 593-5). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels, found in the thalamus area, are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam. Ezogabine/retigabine opens KCNQ/Kv7 voltage-gated potassium channels.

GABA_A receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on GABA₃ presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutamnergic transmission is decreased by felbamate that blocks NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam also blocks AMPA/kainate receptors. Levetiracetam binds to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly results in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.
for 3 days; 15 units/m² in the morning for 3 days; 10 units/m² in the morning for 3 days; and 10 units/m² every other morning for 6 days, then stop). The increase in price of ACTH gel in the United States has led many physicians to use the lower-dose regimen because it may be just as effective (initial: 20 units/day for 2 wk, if patient responds, taper and discontinue over a 1-wk period; if patient does not respond, increase dose to 30 units/day for 4 wk then taper and discontinue over a 1-wk period). Response is usually observed within the 1st 7 days; however, if no response is observed within 2 wk, the lot is changed. During the tapering period of any regimen, and especially in symptomatic patients, relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 wk and then beginning the taper again. Synthetic ACTH has also been used: Synacthen Depot intramuscular 0.25 mg/ml or 1 mg/ml is used; 1 mg is considered to have the potency of 100 IU in stimulating the adrenal gland.

Awake and asleep EEGs are often done 1, 2, and 4 wk after the initiation of ACTH to monitor the patient’s response, with the aim of clearing the EEG from hyperrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. All should be carefully monitored for and prophylactic therapy for ulcers is desirable. ACTH is generally thought to offer an added advantage, particularly in cryptogenic cases, over vigabatrin and possibly over prednisone and other steroids.

Vigabatrin is considered by some as a drug of second choice for infantile spasms and by some even as an alternative to ACTH as a drug of first choice. Its principal side effect is retinal toxicity that is seen in approximately 30% of the patients, with resultant visual field defects that persist despite withdrawal of the drug. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications, including valproate, benzodiazepines like nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide, pyridoxine, ketogenic diet, and intravenous gamma globulin (IVIG). None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with cryptogenic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in Lennox-Gastaut syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic atactic seizures), valproate, lamotrigine, topiramate, clobazam, felbamate, and rufinamide are considered to be effective. Felbamate is used as a last resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic–clonic, atypical absence, other tonic, myoclonic) as well. For patients who have a predilection for atypical absence seizures, lamotrigine or ethosuximide are often suitable drugs to try because they are relatively less toxic than many of the alternative drugs. Valproate is helpful against these seizures, too. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling, and often tolerance to its antiepileptic effects develops in a few months. Consequently, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation). In resistant cases of Lennox-Gastaut syndrome and related epilepsies, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, ketogenic diet, or IVIG can be used.

Dravet syndrome is usually treated with valproate and benzodiazepines such as clobazam or clonazepam. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam, but doses need to be adjusted, since stiripentol can increase clobazam levels and valproate can increase stiripentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, and phenytoin are reported to exacerbate seizures. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

Very rare cases of patients who have neonatal, infantile, or early childhood seizures who have pyridoxine-dependent epilepsy (demonstrated to be caused by antiquitin gene mutation) respond to pyridoxine 10-100 mg/day orally (up to 600 mg/day has been used) within 3-7 days of the initiation of oral therapy and almost immediately if given parenterally. Some patients have seizures that are intractable from onset, but others have seizures that show an initial but transient response to traditional AEDs. Some of these patients also require concurrent folinic acid (5-15 mg/day). Other patients require the active form of vitamin B₆, specifically, pyridoxal phosphate (50 mg/day initial dose that can be increased gradually up to 15 mg/kg every 6 hr) owing to their deficiency of PNPO. In both the PNPO-deficient/pyridoxal phosphate–dependent and the pyridoxine-dependent forms, hypotonia and hypopnea can occur after initiation of vitamin therapy. Pyridoxine has also been used by some, specifically in Japan, early in the treatment of West syndrome. Patients with cerebral folate deficiency can respond to folinic acid supplementation (usually at doses of 2-3 mg/kg/day). Traditionally these entities have been diagnosed by giving the vitamin B₆, or folinic acid in therapeutic trials, but currently laboratory testing is available to confirm the diagnosis (see Chapter 593.4).

Absence seizures are most often initially treated with ethosuximide, which is, as effective as, but less toxic than, valproate and more effective than lamotrigine. Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic–clonic seizures coexist with absence seizures, as these 2 medications are effective against the latter seizures whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents’ observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic–clonic and absence seizures. Benzodiazepines, clonazepam, lamotrigine, and topiramate are alternatives for the treatment of benign myoclonic epilepsy. Severe myoclonic epilepsies are treated with medications effective for Lennox-Gastaut syndrome such topiramate, clobazam, and valproate, as well as zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Partial and secondary generalized tonic and clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, pheno-barbital, topiramate, valproic acid, lamotrigine, clobazam, or clonazepam (see Table 593-8). Oxcarbazepine, levetiracetam, carbamazepine (United States), or valproate (Europe) are often being used first. One study favored lamotrigine as initial monotherapy for partial seizures whereas ethosuximide and valproate for generalized seizures. Almost any of these medications has been used as first or second choice, depending on the individualization of the therapy.

**CHOICE OF DRUG: OTHER CONSIDERATIONS**

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated below.

**Comparative effectiveness** (Table 593-11) and potential for paradoxical seizure aggravation by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered.

**Comparative tolerability** (see Table 593-14): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 yr of age, on polytherapy, and/or have metabolic disorders. Thus, if metabolic disorders are suspected, other drugs should be considered first and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate,
ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: ≥1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blind or open-label study or 1 class IV clinical study or data from expert committee reports, opinions from experienced clinicians. FDA, Food and Drug Administration; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide. Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al: Treatment of pediatric epilepsy: European expert opinion, Epileptic Disord 9:353–412, 2007, and Perucca E, Tomson T, ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 54(3):551–563, 2013.

* Ease of initiation of the AED: Medications that are started very gradually such as lamotrigine and topiramate should not be chosen in situations when there is a need to achieve a therapeutic level quickly. In such situations, medications that have intravenous preparations or that can be started and titrated more quickly, such as valproate, phenytoin, or levetiracetam, should be considered instead.

* Drug interactions and presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications like gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate. It also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction, and, thus, the free and not the total level needs to be checked when both medications are being used together. Enzyme inducers like phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate and zonisamide. Medications exclusively excreted by the kidney like levetiracetam and gabapentin are not subject to such interactions.
The presence of comorbid conditions: For example, the presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions such as valproate or topiramate. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases appetite such as topiramate might be used instead. In adolescent girls of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations (Table 593-12). Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ mutations (POLG) with mitochondrial DNA depletion (also known as Alpers-Huttenlocher syndrome), other mitochondrial disorders (Leigh syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy-myopathy-sensory ataxia syndrome), and hyperammonemnic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy.

Coexisting seizures: In a patient with both absence and generalized tonic–clonic seizures, a drug that has a broad spectrum of antiseizure effects such as lamotrigine or valproate could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.

History of prior response to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to carbamazepine, carbamazepine could be a desirable choice.

Mechanism of drug actions: At present, the current understanding of the pathophysiology of epilepsy does not allow specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, in general, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.

Ease of use: Medications that are given once or twice a day are easier to use than medications that are given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role.

Ability to monitor the medication and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications also require blood level monitoring for optimal titration. However, monitoring in itself can represent a practical or patient satisfaction disadvantage for the older drugs as compared to the newer AEDs, which generally do not require blood-level monitoring except to check for compliance.

Patient’s and family’s preferences: All things being equal, the choice between 2 or more acceptable alternative AEDs might also depend on the patient’s or family’s preferences. For example, some patients might want to avoid gingival hyperplasia and hirsutism as side effects but might tolerate weight loss, or vice versa.

Genetics and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. For example, there is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, South East Asian populations; hence these AEDs should be avoided in genetically susceptible persons after testing for the allele. The testing for other alleles that predispose to such allergies in other populations is not yet clinically useful. Mutations of the SCN1A sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, and phenytoin, and to the use of the more appropriate valproate, clobazam, or stiripentol.

### Table 593-12: Teratogenesis and Perinatal Outcomes of Antiepileptic Drugs

<table>
<thead>
<tr>
<th>FINDING</th>
<th>RECOMMENDATION</th>
<th>LEVEL OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA as part of polytherapy and possibly monotherapy probably contributes to the development of major congenital malformations and adverse cognitive outcome</td>
<td>If possible, avoidance of valproate polytherapy during the 1st trimester of pregnancy should be considered so as to decrease the risk of major congenital malformations and adverse cognitive outcome</td>
<td>B</td>
</tr>
<tr>
<td>AED polytherapy, as compared to monotherapy, regimens probably contribute to the development of major congenital malformations and to adverse cognitive outcomes</td>
<td>If possible, avoidance of AED polytherapy during the 1st trimester of pregnancy should be considered to decrease the risk of major congenital malformations and adverse cognitive outcome</td>
<td>B</td>
</tr>
<tr>
<td>Monotherapy exposure to phenytoin or phenobarbital possibly increases the likelihood of adverse cognitive outcomes</td>
<td>If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent adverse cognitive outcomes</td>
<td>C</td>
</tr>
<tr>
<td>Neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1 min Apgar score of &lt;7</td>
<td>Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (level B) and possibly at increased risk of 1 min Apgar scores of &lt;7</td>
<td>C</td>
</tr>
</tbody>
</table>

Levels of recommendation: A: strongest recommendation; based on class 1 evidence; B and C: lower levels of recommendations.

Types of malformations: Prior studies had reported the occurrence of spina bifida with valproate and carbamazepine therapy, and of cardiac malformation and cleft palate after carbamazepine, phenytoin, and phenobarbital exposure. There is variability from study to study. However, in general the relative incidence of major malformations of approximately 10% for valproate monotherapy, higher with valproate polytherapy, and in the range of 5% for monotherapy with the other above 3 AEDs and higher with polytherapy.

FDA categories: Valproate, phenobarbital, carbamazepine, and phenytoin are classified by the FDA as category D. Ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are category C. Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: Studies, adequate, well-controlled, or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy might outweigh the potential risk.

AED, antiepileptic drug; VPA, valproate.

In nonemergency situations, or when loading is not necessary, the **maintenance dose** of the chosen AED is started (Table 593-13). With some medications (e.g., carbamazepine and topiramate), even smaller doses are initially started then **gradually increased** up to the maintenance dose to build tolerance to adverse effects such as sedation. For example, the starting dose of carbamazepine is usually 5-10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and a therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose to build tolerance to adverse effects such as sedation. For valproate it is 25 mg/kg, for phenytoin it is 20 mg/kg, and for phenobarbital it is 10-20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hr), to avoid excessive sedation.

Only 1 drug should be used initially and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and the initial drug subsequently tapered. Control with 1 drug may be achieved faster, a **loading dose** may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate it is 25 mg/kg, for phenytoin it is 20 mg/kg, and for phenobarbital it is 10-20 mg/kg. Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs such as phenytoin, carbamazepine, valproate, fenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2-7 days (half-life: 6-24 hr). For phenobarbital, it is 2-4 wk (mean half-life: 69 hr). For zonisamide it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hr in monotherapy and 27-38 hr during combination therapy with enzyme inducers).

**Table 593-13 Dosages of Selected Antiepileptic Drugs**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>FDA APPROVAL (AGE APPROVED)</th>
<th>MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED</th>
<th>USUAL DOSING</th>
<th>THERAPEUTIC LEVELS</th>
<th>PREPARATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Absence seizures (adults)</td>
<td>1-12 mo; 10 &lt;1 yr: 20-30 bid or tid</td>
<td>10-15 mg/L</td>
<td>125, 250, 500 mg tabs</td>
<td></td>
</tr>
<tr>
<td>Bromide</td>
<td></td>
<td>50-100 bid or qd</td>
<td>10-15 mEq/L</td>
<td>Supplied as triple bromide soln (240 mg/mL of bromide salt)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine†</td>
<td>Partial and GTC (all ages)</td>
<td>10-20 tid or qid SR usually bid</td>
<td>3-12 mg/L</td>
<td>150, 300 mg ER caps 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs 100 mg/5 mL susp</td>
<td></td>
</tr>
<tr>
<td>Clonazepam‡</td>
<td>Absence sz, LGS, myoclonic sz (all ages)</td>
<td>0.05-0.2 bid or tid</td>
<td>25-85 µg/L</td>
<td>0.5, 1, 2 mg tabs 0.125, 0.25, 0.5 mg orally disintegrating tabs</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Partial sz (all ages &gt;6 mo)</td>
<td>0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age; see Table 593-15) bid or tid</td>
<td>100-700 µg/L</td>
<td>2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Absence sz (&gt;3 yr)</td>
<td>20-30 bid or tid</td>
<td>40-100 mg/L</td>
<td>250 mg caps 250 mg/5 mL syrup, soln</td>
<td></td>
</tr>
<tr>
<td>Ezogabine</td>
<td>Partial sz (adults)</td>
<td>No pediatric dose approved tid</td>
<td>—</td>
<td>50, 200, 300, 400 mg tabs</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>LGS (&gt;2 yr) Partial sz (&gt;14 yr)</td>
<td>15-45 bid or tid</td>
<td>50-110 mg/L</td>
<td>400, 600 mg tabs 600 mg/5 mL susp</td>
<td></td>
</tr>
<tr>
<td>Gabapentin‡</td>
<td>Partial sz (&gt;3 yr)</td>
<td>30-60 tid</td>
<td>2-20 mg/L</td>
<td>100, 300, 400 mg caps, 600, 800 mg tabs</td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Partial sz (&gt;17 yr)</td>
<td>No FDA approved dose. 4-12 bid</td>
<td>&lt;= 15 µg/L</td>
<td>50, 100, 150, 200 mg tabs 10 mg/mL oral soln</td>
<td></td>
</tr>
</tbody>
</table>
Table 593-13  Dosages of Selected Antiepileptic Drugs—cont’d

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>FDA APPROVAL (AGE APPROVED)</th>
<th>MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED</th>
<th>USUAL DOSSING</th>
<th>THERAPEUTIC LEVELS</th>
<th>PREPARATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>LGS, partial and tonic–clonic sz (age &gt;2 yr)</td>
<td>5-15&lt;sup&gt;§&lt;/sup&gt; 1-5&lt;sup&gt;§&lt;/sup&gt;</td>
<td>tid bid</td>
<td>1-15 mg/L</td>
<td>25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs</td>
</tr>
<tr>
<td>Levetiracetam&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Myoclonic, partial and tonic–clonic sz (age &gt;4-6 yr)</td>
<td>20-40</td>
<td>bid or tid</td>
<td>6-20 mg/L</td>
<td>250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Status epilepticus (all ages)</td>
<td>0.05-0.1</td>
<td>bid or tid</td>
<td>20-30 µg/L</td>
<td>0.5, 1, 2 mg tabs 2 mg/mL soln</td>
</tr>
<tr>
<td>Methsuximide (or methsuximide)</td>
<td>Absence sz (children and older)</td>
<td>10-30</td>
<td>bid or tid</td>
<td>10-50 mg/L</td>
<td>150, 300 mg caps</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>–</td>
<td>0.25-1</td>
<td>bid or tid</td>
<td>&lt;200 µg/L</td>
<td>5 mg tabs</td>
</tr>
<tr>
<td>Oxcarbazepine&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Partial sz (&gt;2 yr)</td>
<td>20-40</td>
<td>bid</td>
<td>13-28 mg/L</td>
<td>150, 300, 600 mg tabs 300 mg/5 mL susp</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Partial sz (&gt;12 yr)</td>
<td>2-12 mg per day (older than 12 yr)</td>
<td>qhs</td>
<td>-</td>
<td>2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tabs</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Myoclonic, partial, and tonic–clonic sz and status (all ages)</td>
<td>&lt;3 yr, 3-5 &gt;5 yr, 2-3</td>
<td>bid or qd</td>
<td>10-40 mg/L</td>
<td>15, 30, 60, 90, 100 mg tabs 4 mg/mL soln</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Partial, tonic–clonic sz and status (all ages)</td>
<td>&lt;3 yr, 8-10 &gt;3 yr, 4-7</td>
<td>tabs, susp: tid caps: qd</td>
<td>5-20 mg/L</td>
<td>50 mg tabs 30,100 mg caps 125 mg/5 mL susp</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Partial sz (adults)</td>
<td>2-14</td>
<td>bid</td>
<td>Up to 10 µg/mL</td>
<td>25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln</td>
</tr>
<tr>
<td>Primidone</td>
<td>Partial and tonic–clonic sz (all ages)</td>
<td>10-20</td>
<td>bid or tid</td>
<td>4-13 mg/L</td>
<td>50, 250 mg tabs, susp</td>
</tr>
<tr>
<td>Rufinamide&lt;sup&gt;†&lt;/sup&gt;</td>
<td>LGS (age &gt;4 yr)</td>
<td>30-45</td>
<td>bid</td>
<td>&lt;60 µg/mL</td>
<td>200, 400 mg tabs</td>
</tr>
<tr>
<td>Sulthiame&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>5-15</td>
<td>bid or tid</td>
<td>1.5-20 µg/mL</td>
<td>50, 200 mg caps Not available in all countries</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Partial sz (age &gt;2 yr)</td>
<td>0.5-2</td>
<td>bid, tid, qid</td>
<td>80-450 µg/L</td>
<td>2, 4, 12, 16 mg tabs</td>
</tr>
<tr>
<td>Topiramate&lt;sup&gt;†&lt;/sup&gt;</td>
<td>LGS, partial and tonic–clonic sz (all ages)</td>
<td>3-9, slow titration</td>
<td>bid or tid</td>
<td>2-25 mg/L</td>
<td>25, 100, 200 mg tabs 15, 25 mg sprinkle caps</td>
</tr>
<tr>
<td>Valproate</td>
<td>Absence, myoclonic, partial and tonic–clonic sz (age &gt;2 yr)</td>
<td>15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day)</td>
<td>Sprinkle caps: bid Soln: tid</td>
<td>50-100 mg/L</td>
<td>250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Infantile spasms and partial sz (age &gt;1 mo)</td>
<td>50-150</td>
<td>bid</td>
<td>20-160 µg/mL</td>
<td>500 mg tabs 500 mg powder for soln</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Partial sz (age &gt;16 yr)</td>
<td>4-8</td>
<td>bid or qd</td>
<td>10-40 mg/L</td>
<td>100 mg caps</td>
</tr>
</tbody>
</table>

Unless specified otherwise, as above, one would usually target the lower range of therapeutic dose then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

<sup>§</sup>Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.
<sup>†</sup>Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.
<sup>‡</sup>Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.
<sup>‡</sup>Child on enzyme inducers.
<sup>†</sup>Available in some European countries.
<sup>‡</sup>Child on valproate.
cap, capsule; ER, extended release; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.
### Table 593-14  Some Common Adverse Effects of Antiepileptic Drugs

<table>
<thead>
<tr>
<th>ANTIEPILEPTIC DRUG</th>
<th>SIDE EFFECT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Nuisance: dizziness, polyuria, electrolyte imbalance. Serious: Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions. Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity</td>
</tr>
<tr>
<td>Bromide</td>
<td>Nuisance: irritability, spurious hyperchloremia (falsely high chloride owing to bromide). Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria. Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity</td>
</tr>
<tr>
<td>Ezogabine</td>
<td>Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria. Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness. Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children &gt;2 yr with complex neurological disorders)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>In children: acute onset of aggression, hyperactivity. In adults: euphoria and behavioral disinhibition, weight gain</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Nuisance: dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder. Serious: possibly cardiac arrhythmias (if predisposed)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs. Serious: Stevens-Johnson syndrome, rarely liver toxicity</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs. In children: behavioral symptoms are common. In adults: depressive mood</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder</td>
</tr>
<tr>
<td>Phenobarbital and</td>
<td>Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts. Serious: liver toxicity, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>other barbiturates</td>
<td></td>
</tr>
<tr>
<td>Phenytoin and other</td>
<td>Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia). Serious: Stevens-Johnson syndrome, liver toxicity</td>
</tr>
<tr>
<td>Hydantoins</td>
<td>Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia. Serious: hypersensitivity reactions, rhabdomyolysis</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression). Serious: liver toxicity, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Primidone</td>
<td>Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures. Serious: precipitation of nonconvulsive status epilepticus</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Nuisance: somnolence, vomiting. Serious: contraindicated in familial short QT interval</td>
</tr>
<tr>
<td>Succinimides</td>
<td>Nuisance: nausea, abdominal discomfort, anorexia, hiccups. Serious: Stevens-Johnson syndrome, drug-induced lupus</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures. Serious: precipitation of nonconvulsive status epilepticus</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Nuisance: cognitive dysfunction, weight loss, renal calculi, hypohidrosis, fever. Serious: precipitation of glaucoma</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities. Serious: hepatic and pancreatic toxicity</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Nuisance: hyperactivity. Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow up</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever</td>
</tr>
</tbody>
</table>

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions.

AED, antiepileptic drug; CNS, central nervous system.
multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess response for absence seizures, as the EEG mirrors response in such patients.

**Monitoring**

For the older AEDs, before starting treatment, baseline laboratory studies, including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on, because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the 1st 3-6 mo of therapy. These laboratory studies are usually initially checked once or twice during the 1st mo, then every 3-4 mo thereafter. Serious concerns have been raised about the real usefulness of routine monitoring (in the absence of clinical signs) because the yield of significant adverse effects is low and the costs may be high. There are currently many advocates of less-frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients on carbamazepine or on phenytoin. This adverse effect responds to decreasing the dose or to stopping the medication and should be distinguished from the much-less-common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and of blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 yr of age with complex neurological disorders who are on the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or change of medication. Allergic rash can occur with any medication, but is probably most common with lamotrigine, carbamazepine, and phenytoin.

**SIDE EFFECTS**

During follow-up the patient should be monitored for side effects. Occasionally, a Stevens-Johnson–like syndrome develops, probably most commonly with lamotrigine; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking carbamazepine and lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce 25-hydroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients on chronic AED therapy because it is often associated with vitamin D abnormalities (low bone density, rickets, and hypocalcemia) in children and adults, particularly those on enzyme-inducing medications. Thus, counseling the patient about sun exposure and vitamin D intake, monitoring its levels, and, in most cases, vitamin D supplementation are recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 400-2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 yr old) who are on valproate in combination with other AEDs, particularly those who might have inborn errors of metabolism such as acidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The FDA has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications. This is obviously more applicable to adolescents and adults.

When adding a new AED, the doses used are often affected by the background medications. For example, if the patient is on enzyme inducers, the doses needed of valproate and lamotrigine are often double the usual maintenance doses. On the other hand, if the patient is on valproate, the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Thus, changes in the dosing of the background medication are often done as the interacting medication is being started. Genetic variability in enzymes that metabolize AEDs, and in the presence of inducible multidrug resistance genes, pharmacogenomics, might account for some of the variation among individuals in responding to certain AEDs. Although numerous variants of the cytochrome P450 enzymes have been characterized and although several multidrug resistance genes have been identified, the use of this new knowledge is currently largely restricted to research investigations, and it has yet to be applied in routine clinical practice.

**Additional Treatments**

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug or dual (combination) therapy is considered.

Patients with drug-resistant (previously referred to as intractable or refractory) epilepsy (those who have failed at least 2 fair trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see Chapter 593.2) and to investigate them for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as intractable epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; folic acid–responsive seizures (demonstrated to be the same disorder as pyridoxine-dependent epilepsy); cerebral folate deficiency; neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy and neonatal diabetes; and hyperinsulinemia–hyperammonia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

**Steroids**, usually given as ACTH (see the discussion of West syndrome in “Severe Generalized Epilepsies” in Chapter 593.4) or as prednisone 2 mg/kg/day (or equivalent), are often used in epileptic encephalopathies such as West, Lennox-Gastaut, myoclonic astatic, continuous spike-waves in slow-wave sleep, and Landau-Kleffner syndromes. The course usually is for 2-3 mo with a taper over a similar period. Because relapses occur commonly during tapering, and in such syndromes as Landau-Kleffner and continuous spike-waves in slow-wave sleep therapy for longer than 1 yr is often needed.

IVIG has also been reported to be similarly effective in nonimmunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike-waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions, because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion. Low IgA, low IgG2, and male sex are reported to possibly predict favorable response. The usual regimen is 2 g/kg divided over 4 consecutive days followed by 1 g/kg once a month for 6 mo. The mechanism of action of steroids and of IVIG is not known but is presumed to be antiinflammatory, because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The **ketogenic diet** is believed to be effective in glucose transporter protein 1 deficiency, pyruvate dehydrogenase deficiency, myoclonic-astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also suggestion of possible efficacy in selected
mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary); carnitine palmitoyletransfaerase 1 or II deficiency; carnitine translocase deficiency; β-oxidation defects; medium-chain acyl dehydrogenase deficiency; long-chain acyl dehydrogenase deficiency; short-chain acyl dehydrogenase deficiency; long-chain 3-hydroxyacyl-coenzyme A deficiency; medium-chain 3-hydroxyacyl-coenzyme A deficiency; pyruvate carboxylase deficiency; and porphyrias. Thus, an appropriate metabolic work-up, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile; total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3:1 or 4:1 fat:nonfat ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic-index diet and the Atkins diet are easier to institute, do not require hospitalization, and are also useful, but it is not known yet if they are as effective as the classic diet.

**APPROACH TO EPILEPSY SURGERY**

If a patient has failed 3 drugs, the chance of achieving seizure freedom using AEDs is generally <10%. Therefore, proper evaluation for surgery is necessary as soon as patients fail 2 or 3 AEDs, usually within 2 yr of the onset of epilepsy and often sooner than 2 yr. Performing epilepsy surgery in children at an earlier stage (e.g., <5 yr of age) allows transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably non-toxic doses; absence of expected unacceptable adverse consequences of surgery, and a properly defined epileptogenic zone (area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis, by an expert team of epilepsy specialists in an epilepsy center, of the following parameters: seizure semiology, interictal EEG, video-EEG long-term monitoring, neuropsychologic profile, and MRI. Other techniques, such as invasive EEG (depth electrodes, subdural strips), single-photon emission CT, magnetoencephalography, and positron emission tomography are also often needed when the epileptogenic zone is difficult to localize or when it is close to eloquent cortex. To avoid resection of eloquent cortex, several techniques can be used, including the **Wada test**. In this test, intracarotid infusion of amobarbital is used to anesthetize 1 hemisphere to lateralize memory and speech by testing them during that unilateral anesthesia. Other tests to localize function include functional MRI, magnetoencephalography, and subdural electrodes with cortical stimulation. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes EEG monitoring, imaging, and age-specific neuropsychologic assessment.

Epilepsy surgery is often used to treat refractory epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, Landau-Kleffner syndrome, and hemispheric syndromes, such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with intractable epilepsy resulting from metabolic or degenerative problems are not candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. Hemispherectomy is used for diffuse hemispheric lesions; **multiple subpial transection**, a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in eloquent cortex such as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used for drop attacks. **Vagal nerve stimulation** is often used for intractable epilepsies of various types and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery. Focal resection and hemispherectomy result in a high rate (50-80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates (5-10%) of seizure freedom; however, these procedures do result in significant reductions in the frequency and severity of seizures, decrease in medication requirements, and meaningful improvements in the patient’s quality of life in approximately half or more of eligible patients.

**DISCONTINUATION OF THERAPY**

Discontinuation of AEDs is usually indicated when children are free of seizures for at least 2 yr. In more-severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom on treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 mo.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 yr or longer and who have a normal EEG when AED withdrawal is initiated, remain free of seizures after discontinuing medication, and most relapses occur within the 1st 6 mo.

Certain risk factors can help the clinician predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign genetic (idiopathic) epilepsy. In patients with absences or in patients treated with valproate for primary generalized epilepsy, the risk of relapse might still be high despite a normal EEG because valproate can normalize EEGs with generalized spike-wave abnormalities. Thus, in these patients, repeating the EEG during drug taper can help identify recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than 1 AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually; often over a period of 3-6 mo. Abrupt discontinuation can result in withdrawal seizures or status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2-3 mo after AEDs are completely discontinued indicate relapse, and resumption of treatment is usually warranted.

The decision to attempt AED withdrawal must be assessed mutually among the clinician, the parents, and the child depending on the child’s age. Risk factors should be identified and precautionary measures should be taken. The patient and family should be counseled fully on what to expect, what precautions to take (including cessation of driving for a period of time), and what to do in case of relapse. A prescription for rectal diazepam or of intranasal midazolam to be given at the time of AED withdrawal based on the type of epilepsy syndrome and etiology; the important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign genetic (idiopathic) epilepsy. In patients with absences or in patients treated with valproate for primary generalized epilepsy, the risk of relapse might still be high despite a normal EEG because valproate can normalize EEGs with generalized spike-wave abnormalities. Thus, in these patients, repeating the EEG during drug taper can help identify recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than 1 AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

**Sudden Unexpected Death in Epilepsy**

SUDEP is the most common epilepsy related mortality in patients with chronic epilepsy; the incidence is unknown but ranges from 1-5 per 1,000 people with epilepsy. Although the precise etiology is unknown, risk factors include polypharmacology, poorly controlled generalized tonic–clonic seizures, male gender, age younger than 16 yr, long duration of epilepsy, and frequent seizures. Patients are usually found dead in their bed in a prone position with evidence suggesting a recent seizure. Potential mechanisms of SUDEP include respiratory arrest or dysfunction, drug-induced cardiac toxicity, CNS dysfunction (hypventilation, arrhythmia, suppression of brain electrical activity), or pulmonary edema. Table 593-15 lists possible preventive measures.

Bibliography is available at Expert Consult.
Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period in life: 57.5 per 1,000 in infants with birth weights <1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g have seizures.

**PATHOPHYSIOLOGY**

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these are delay in Na+/K+/2Cl− influx and hyperpolarization. This phenomenon appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures. The reason for this is that the Cl− transporter, NKCC1, is predominantly expressed in the neonatal period, leading to transport of Cl− into the cell at rest, and then to cellular depolarization upon activation of GABA_A receptors and opening of Cl− channels with chloride efflux. This is important for neuronal development but renders the neonatal brain hyperexcitable. With maturation, expression of NCCK1 decreases and KCC2 increases. KCC2 transports Cl− out of the cell, resulting in reduction of intracellular chloride concentration so that when GABA_A receptors are activated, Cl− influx and hyperpolarization occur. Bumetanide, a diuretic that blocks NKCC1, can prevent excessive GABA depolarization and avert the neuronal hyperexcitability underlying neonatal seizures. It also prevents, in rats, complex febrile seizure hyperactivation of excitatory GABA_A receptors and the resultant granule cell ectopia and temporal lobe epilepsy.

Although it is susceptible to developing seizures, the immature brain appears to be more resistant to the deleterious effects of seizures than the mature brain, as a result of increases in calcium binding proteins that buffer injury-related increases in calcium, increased extracellular space, decreased levels of the second messenger inositol triphosphate, and the immature brain’s ability to tolerate hypoxic conditions by resorting to anaerobic energy metabolism.

Many animal studies indicate that seizures are detrimental to the immature brain. Human studies also suggest harmful effects of seizures as shown by MRI and by the association of worse prognosis in neonates with seizures even when correcting for confounding factors. Even electrographic seizures without clinical correlates have been shown to be associated with worse prognosis. However, it is not definite that this association is causal: It is difficult in human studies to distinguish among effects of seizures, of the underlying insult responsible for the seizures (clinical or electrographic), and of the AEDs used to stop the seizures. Most physicians currently believe that it is favorable to control clinical as well as electrographic seizures.

**TYPES OF NEONATAL SEIZURES**

There are 5 main neonatal seizure types: subtle, clonic, tonic, spasms, and myoclonic. Spasms, focal clonic, focal tonic, and generalized myoclonic seizures are, as a rule, associated with electrographic discharges (epileptic seizures), whereas motor automatisms, the subtle, generalized tonic and multifocal myoclonic episodes are frequently not associated with discharges and thus are thought to often represent release phenomena with abnormal movements secondary to brain injury rather than true epileptic seizures (Table 593-16). To determine clinically whether such manifestations are seizures or release phenomena is often difficult, but precipitation of such manifestations by stimulation and aborting them by restraint or manipulation would suggest that they are not seizures. One needs to keep in mind, however, that epileptic seizures can also be induced by stimulation. Thus, in many cases, specifically in sick neonates with history of neurologic insults, continuous bedside EEG monitoring helps make this distinction. Such monitoring has become the standard of care in most intensive care nurseries.

**Subtle Seizures**

Subtle seizures include transient eye deviations, nystagmus, blinking, mouthing, abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping), fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.

**Clonic Seizures**

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a nonjacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period presumably due to decreased connectivity associated with incomplete myelination at this age.

**Tonic Seizures**

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of trunk or neck in an asymmetric way often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extension or tonic flexion of upper extremities often associated with tonic extension of lower extremities.

**Spasms**

Spasms are sudden generalized jerks lasting 1-2 sec that are distinguished from generalized tonic spells by their shorter duration and by
the fact that spasms are usually associated with a single, very brief, generalized discharge.

**Myoclonic Seizures**
Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 msec) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

**Seizures vs Jitteriness**
Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures, on the other hand, generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Also unlike jitteriness, seizures often involve eye deviation and autonomic changes.

**Etiology**
Table 593-17 lists causes of neonatal seizures.

**Hypoxic–Ischemic Encephalopathy**
This is the most common cause of neonatal seizures, accounting for 50-60% of patients. Seizures secondary to this encephalopathy occur within 12 hr of birth.

**Vascular Events**
These include intracranial bleeds and ischemic strokes and account for 10-20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinial matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure and these can be
Infections, particularly herpes simplex encephalitis.

Neonatal seizures and include bacterial meningitis, TORCH (Toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections, particularly herpes simplex encephalitis.

**Brain Malformations**

Brain malformations account for 5-10% of neonatal seizure cases. An example is **Aicardi syndrome**, which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

**Metabolic Disturbances**

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency.

**Hypoglycemia** can cause neurologic disturbances and is very common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

**Hypocalcemia** occurs at 2 peaks. The first peak corresponds to low-birthweight infants and is evident in the 1st 2-3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hyponatremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion.

**Local anesthetic intoxication** seizures can result from neonatal intoxication with local anesthetics administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic work-up (see Chapter 593.2) including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very-long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine for organic acids, α-aminoadipic acid semialdehyde and sulfoacycsteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α-aminoadipic acid semialdehyde, pyridoxal phosphate, 5-MTHF (5-methyltetrahydrofolate), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups that these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia**, for example, requires measuring the ratio of CSF glycine to plasma glycine.

**Pyridoxine** and **pyridoxal dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the 1st few hr of life. Cognitive impairment is often associated if therapy is delayed (see Chapter 593.6).

**Drug Withdrawal**

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal. Such drugs include narcotic analgesics, sedative-hypnotics, and others. The associated seizures appear during the 1st 3 days of life.

**Neonatal Seizure Syndromes**

Seizure syndromes include **benign infantile neonatal seizures (fifth day fits)**, which are usually apneic and focal motor seizures that start around the fifth day of life. Interictal EEG shows a distinctive pattern called **theta pointu alternant** (runs of sharp 4-7 Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have onset at 2-4 days of age and usually remit at 2-15 wk of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by mutations in the KCNQ2 and KCNQ3 genes. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy** (Ohtahara syndrome) are discussed in Chapter 593.4.

<table>
<thead>
<tr>
<th>Table 593-17</th>
<th>Causes of Neonatal Seizures According to Common Age of Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGES 1-4 DAYS</strong></td>
<td></td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Drug withdrawal, maternal drug use of narcotic or barbiturates</td>
<td></td>
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<tr>
<td>Drug toxicity: lidocaine, penicillin</td>
<td></td>
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<tr>
<td>Intraventricular hemorrhage</td>
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<tr>
<td>Acute metabolic disorders</td>
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<td>Hypocalcemia</td>
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<td>Sepsis</td>
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<tr>
<td>Maternal hyperthyroidism, or hypoparathyroidism</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Perinatal insults, prematurity, small for gestational age</td>
<td></td>
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<tr>
<td>Maternal diabetes</td>
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<tr>
<td>Hyperinsulinemic hypoglycemia</td>
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<tr>
<td>Hypomagnesemia</td>
<td></td>
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<tr>
<td>Hyponatremia or hypernatremia</td>
<td></td>
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<tr>
<td>Iatrogenic or inappropriate antidiuretic hormone secretion</td>
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<tr>
<td>Inborn errors of metabolism</td>
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<td>Galactosemia</td>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Urea cycle disorders</td>
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<tr>
<td>Pyridoxine deficiency and pyridoxal-5-phosphate deficiency must be considered at any age</td>
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<tr>
<td><strong>AGES 4-14 DAYS</strong></td>
<td></td>
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<tr>
<td>Infection</td>
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<tr>
<td>Meningitis (bacterial)</td>
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<td>Encephalitis (enteroviral, herpes simplex)</td>
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<tr>
<td>Metabolic disorders</td>
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<td>Hypocalcemia</td>
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<td>Diet, milk formula</td>
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<td>Hypoglycemia, persistent</td>
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<td>Inherited disorders of metabolism</td>
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<td>Galactosemia</td>
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<td>Fructosemia</td>
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<td>Leucine sensitivity</td>
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<td>Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome</td>
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<td>Beckwith syndrome</td>
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<td>Drug withdrawal, maternal drug use of narcotics or barbiturates</td>
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<td>Benign neonatal convulsions, familial and nonfamilial</td>
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<td>Kernicterus, hyperbilirubinemia</td>
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<td>Developmental delay, epilepsy, neonatal diabetes syndrome</td>
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<td><strong>AGES 2-8 WK</strong></td>
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<td>Infection</td>
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<td>Herpes simplex or enteroviral encephalitis</td>
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<td>Head injury</td>
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<td>Subdural hemotoma</td>
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<tr>
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<td>Inherited disorders of metabolism</td>
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<td>Aminoacidurias</td>
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<td>Urea cycle defects</td>
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<td>Organic acidurias</td>
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<td>Neonatal adrenoleukodystrophy</td>
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<td>Malformations of cortical development</td>
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<td>Lissencephaly</td>
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<td>Focal cortical dysplasia</td>
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<td>Tuberous sclerosis</td>
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<tr>
<td>Sturge-Weber syndrome</td>
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Diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

**Intracranial Infections**

Bacterial and nonbacterial infections account for 5-10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (Toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections, particularly herpes simplex encephalitis.
Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see Chapter 594).

DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history and performing an adequate physical examination. Depending on the case, additional tests or procedures can be performed. EEG is considered the main tool for diagnosis. It can show paroxysmal activity (e.g., sharp waves) in between the seizures and electrographic seizure activity if a seizure is captured. However, some neonatal seizures might not be associated with EEG abnormalities as noted above either because they are "release phenomena" or alternatively because the discharge is deep and is not detected by the scalp EEG. Additionally, electrographic seizures can occur without observed clinical signs (electroclinical dissociation). This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal motor manifestations. Continuously monitoring the EEG at the bedside in the neonatal intensive care unit for neonates at risk for neonatal seizures and brain injury is part of routine clinical practice in most centers, providing real-time measurements of the brain's electrical activity and identifying seizure activity. Many centers apply EEG monitoring to at-risk babies even before seizures develop, which is often desirable; others monitor patients who have manifested or are suspected of having seizures. In addition, there are currently attempts to develop methods for continuous monitoring of cerebral activity with automated detection and background analysis of neonatal seizures, similar to the continuous ECG monitoring in intensive care facilities. In infants started on hypothermia protocols following suspected hypoxic–ischemic injuries, it is recommended to continuously monitor the EEG during the cooling and rewarming periods to detect clinical and subclinical events in this high-risk population. The American Clinical Neurophysiology Society recommends continuous EEG monitoring in the neonatal intensive care unit to monitor evolution of EEG background to help with prognostication, to guide titration of anticonvulsant therapy for infants with established seizures, to screen for seizures among infants deemed to be at risk (hypoxic ischemic encephalopathy, stroke, meningitis, intraventricular hemorrhage, metabolic disorders, and congenital cerebral malformations), to screen for seizures among infants who are paralyzed, to characterize clinical events suspected to represent seizures, and to detect impending cerebral ischemia or hemorrhage.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the retina might show the presence of choriorretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. The Aicardi syndrome is associated with coloboma of the iris and retinal lacunae. Inspection of the skin might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on UV light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity, DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium, 0.2 mL/kg of a 50% solution of MgSO4. Serum electrolyte measurement can indicate significant hyponatremia (serum sodium <115 mEq/L) or hypernatremia (serum sodium >160 mEq/L) as a cause of the seizure disorder.

A lumbar puncture is indicated in virtually all neonates with seizures, unless the cause is obviously related to a metabolic disorder such as hypoglycemia or hypocalcemia. The latter infants are normally alert interictally and usually respond promptly to appropriate therapy. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the 2 disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many inborn errors of metabolism cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the 1st few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, bulging fontanel, and muscle rigidity during the 1st wk of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include nonketotic hyperglycinemia, an intractable condition characterized by markedly elevated plasma and CSF glycerol levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease suggested by elevated levels of serum and CSF lactate and an increased lactate:pyruvate ratio. Biotinidase deficiency should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part XI, Metabolic Disorders.

Unintentional injection of a local anesthetic into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the 2nd-3rd day of life, with a seizure frequency of 10-20/day. Patients are normal between seizures, which stop in 1-6 mo. These are caused by mutations in the voltage-sensitive potassium channel genes Kv7.2, and Kv7.3 (KCND2 and KCNQ3). Other mutations in the Kv7.2 gene cause severe neonatal epileptic encephalopathy. Fifth-day fits occur on day 5 of life (4-6 days) in normal-appearing neonates. The seizures are multifocal and are often present for <24 hr. The diagnosis requires exclusion of other causes of seizures and sequencing of the above genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin. The history may suggest that similar seizures
occurred in utero. When pyridoxine-dependent seizures are suspected, 100-200 mg of pyridoxine or pyridoxal phosphate should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of IV pyridoxine. Therefore, a 6-wk trial of oral pyridoxine (100-200 mg/day) or preferably pyridoxal phosphate (as pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to IV pyridoxine. Measurement of serum pipecolic acid and α-aminoacidic acid semi-aldehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folic acid) or pyridoxal phosphate (15-60 mg/kg/day). Cerebral folate deficiency should also be ruled out by medication trial (folinic acid 1-3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 593.4). The earlier the therapy is initiated in these vitamin responsive disorders, the more favorable the outcome.

Drug-withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. The incriminated drugs include barbiturates, benzodiazepines, heroin, and methadone. The infant may be jittery, irritable, and lethargic, and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe cytoarchitectural abnormalities of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders. Infants with chromosome abnormalities and adrenoleukodystrophy are also at risk for seizures and should be evaluated with investigation of a karyotype and serum very-long-chain fatty acids, respectively.

**PROGNOSIS**

Over the last few decades, prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care. Mortality has decreased from 40% to 20%. The correlation between EEG and prognosis is very clear. Although neonatal EEG interpretation is very difficult, EEG was found to be highly associated with the outcome in premature and full-term infants. An abnormal background is a powerful predictor of less-favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere also correlate with poorer outcome. The underlying etiology of the seizures is the main determinant of outcome. For example, patients with seizures secondary to hypoxic–ischemic encephalopathy have a 50% chance of developing normally, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

**TREATMENT**

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma), whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of clinical as well electrographic seizures. Others argue for treating clinical seizures only. Most centers favor the first approach. An important consideration before starting anticonvulsants is deciding, based on the severity duration and frequency of the seizures if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply be started on maintenance doses of a long-acting drug. Patients often require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

**Lorazepam**

The initial drug used to control acute seizures is usually lorazepam. Lorazepam is distributed to the brain very quickly and exerts its anticonvulsant effect in <5 min. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hr. Usually, it does not cause hypotension or respiratory depression. The dose is 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hr.

**Diazepam**

Diazepam can be used as an alternative initial drug. It is highly lipophilic, so it distributes very rapidly into the brain and then is cleared very quickly out, carrying the risk of recurrence of seizures. Like other intravenous benzodiazepines, it carries a risk of apnea and hypotension, particularly if the patient is also on a barbiturate, so patients need to be observed for 3-8 hr after administration. The usual dose is 0.1-0.3 mg/kg IV over 3-5 min, given every 15-30 min to a maximum total dose of 2 mg. However, because of the respiratory and blood pressure limitations and because the intravenous preparation contains sodium benzoate and benzoic acid, it is currently not recommended as a first-line agent.

**Midazolam**

Midazolam can be used as an initial drug as a bolus or as a second- or third-line drug as a continuous drip for patients who did not respond to phenobarbital and/or to phenytoin. The doses used have been in the range of 0.05-0.1 mg/kg IV initial bolus, with a continuous infusion of 0.5-1 µg/kg/min IV that can then be gradually titrated upward, if tolerated, every 5 min or longer, to a maximum of approximately 33 µg/kg/min (2 mg/kg/hr).

**Phenobarbital**

Phenobarbital is considered by many as the first choice long-acting drug in neonatal seizures. Whether to use a benzodiazepine first depends on the clinical situation. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 5-10 mg/kg can be given until a dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day usually administered in 2 separate doses. Phenobarbital is metabolized in the liver and is excreted through kidneys. Thus, any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully.

**Phenytoin and Fosphenytoin**

For ongoing seizures, if a total loading dose of 40 mg/kg of phenobarbital was not effective, then a loading dose of 15-20 mg/kg of phenytoin can be administered intravenously. The rate at which the dose should be given must not exceed 0.5-1.0 mg/kg/min so as to prevent cardiac problems, and the medication needs to be avoided in patients with significant heart disease. Heart rate should be monitored while administrating the drug. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Owing to its reduced solubility, potentially severe local cutaneous reactions, interaction with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used.

Fosphenytoin, which is a phosphate ester prodrug, is preferable. It is highly soluble in water, and can be administered very safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 min. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.
Other Medications
Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phentoyin and an additional 15% respond to the second agent. Levetiracetam (which can be given intravenously with later convenient conversion to oral solution) and topiramate (oral) are reported to be the drugs of second and third choice for approximately half of surveyed pediatric neurologists and some have used them even before phenobarbital or phentoyin in selected cases. The dosages used are 10-30 mg/kg/day of levetiracetam, at times higher, and up to 20 mg/kg/day of topiramate. Bumetanide has been used as an adjunct drug, particularly with phenobarbital, because of its effect on the chloride gradient, as discussed above. Lidocaine is another medication used for resistant cases. Primidone, carbamazepine, valproate, and lamotrigine use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 yr of age than in older children.

Duration of Therapy
Duration of therapy is related to the risk of developing later epilepsy in infants suffering from neonatal seizures, which ranges from 10-30% and depends on the individual neurologic examination, the etiology of the seizures, and the EEG at the time of discharge from the hospital. In general, if the EEG at the time of discharge does not show evidence of epileptiform activity, then medications are usually tapered at that time. If the EEG remains paroxysmal, then the decision is usually delayed for several months after discharge.

Bibliography is available at Expert Consult.

593.8 Status Epilepticus
Mohamad A. Mikati and Abeer J. Hani

Status epilepticus is a medical emergency that should be anticipated in any patient who presents with an acute seizure. It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 min as part of an operational definition put forth within the past few years. In the past, the cutoff time was 30 min, but this has been reduced to emphasize the risks involved with the longer durations. The ILAE defines status epilepticus as “a seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without resumption of baseline central nervous system function interictally.” The measures used to treat status epilepticus have to be started in any patient who presents with an acute seizure. It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 min as part of an operational definition put forth within the past few years. The most common type is convulsive status epilepticus (generalized tonic, clonic, or tonic–clonic), but other types do occur, including nonconvulsive status (complex partial, absence), myoclonic status, epilepsy partialis continua, and neonatal status epilepticus. The incidence of status epilepticus ranges between 10 and 60 per 100,000 population in various studies. Status epilepticus is most common in children younger than 5 yr of age, with an incidence in this age group of >100 per 100,000 children.

Approximately 30% of patients presenting with status epilepticus are having their first seizure, and approximately 40% of these later develop epilepsy. Febrile status epilepticus is the most common type of status epilepticus in children. In the 1950s and 1960s, mortality rates of 6-18% were reported after status epilepticus; currently, with the recognition of status epilepticus as a medical emergency, a lower mortality rate of 4-5% is observed, most of it secondary to the underlying etiology rather than to the seizures. Status epilepticus carries an approximately 14% risk of new neurologic deficits, most of this (12.5%) secondary to the underlying pathology.

Nonconvulsive status epilepticus manifests as a confusional state, delirium, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness, catatonia, and or psychotic symptoms. It should be considered in any of these situations, especially in an unresponsive or encephalopathic child. Epilepsia partialis continua has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), and Rasmussen encephalitis.

Refractory status epilepticus is status epilepticus that has failed to respond to therapy, usually with at least 2 (such as a benzodiazepine and another medication) medications. Currently, the trend is not to assign a minimum duration, whereas in the past a minimum duration of 30 min, 60 min, or even 2 hr was cited. New-onset refractory status epilepticus has been identified as a distinct entity that can be caused by almost any of the causes of status epilepticus in a patient without prior epilepsy. It also is often of unknown etiology, presumed to be encephalitic or postencephalitic, can last several weeks or longer, and often, but not always, has a poor prognosis. Devastating epileptic encephalopathy in school-age children, also called fever-induced refractory epileptic encephalopathy in school age children (FIRES) is a syndrome of refractory status epilepticus that is associated with acute febrile infections, appears to be parainfectious in nature, and to be highly drug resistant but responsive to the ketogenic diet.

ETIOLOGY
Etiologies include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol abuse in adolescents; drug withdrawal or overdose in patients on AEDs; hypoglycemia; hypocalcemia; hypotension; hypoglycemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (such as anti-NMDA receptor and anti–voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine and pyridoxal phosphate dependency (these usually present in infancy but childhood onset is also possible); inborn errors of metabolism (see Chapter 593.2) such as nonketotic hyperglycinemia in neonates and mitochondrial encephalopathy with lactic acidosis (MELAS) in infants, children, and adolescents; ion channel–related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections above); hypoxic–ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain tumors; and any other disorders that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, storage diseases).

A rare condition called hemiconvulsion-hemiplegia-epilepsy syndrome consists of prolonged febrile status epilepticus presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition mentioned above called FIRES are likely to be have a parainfectious-autoimmune etiology. Rasmussen encephalitis often causes epilepsy partialis continua (see Chapter 593.3) and sometimes convulsive status epilepticus. Several types of infections are more likely to cause encephalitis with status epilepticus, such as herpes simplex (complex partial and convulsive status). Bartonella (particularly nonconvulsive status), Epstein–Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of status epilepticus, including refractory status epilepticus. HHV6 can cause a distinct epileptic syndrome with limbic status epilepticus in immune-suppressed patients.

MECHANISMS
The mechanisms leading to the establishment of sustained seizure activity seen in status epilepticus appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of GABA_A receptors. This explains the
Bibliography
clinical observation that status epilepticus is often less likely to stop in the next specific period of time the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During status epilepticus there is increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 min, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from status epilepticus. Status epilepticus can cause both neuronal necrosis and apoptosis. The mechanisms of apoptosis are thought to be related to increases in intracellular calcium and proapoptotic factors such as ceramide, Bax, and apoptosis-inducing factor. In addition, inflammation through the cytokines (such as interleukin-1β) released during seizure activity can modify neuronal excitability by modifying neurotransmitter function in a number of ways, such as through phosphorylation of the NR2B subunit rendering the NMDA receptors more permeable to calcium influx, increased expression of highly calcium-permeable AMPA receptors, and induction of endocytosis of GABA<sub>B</sub> receptors. Prostaglandins (such as prostaglandin E<sub>2</sub>) can increase glutamate release and reduce potassium currents leading to increased excitability.

**THERAPY**

Status epilepticus is a medical emergency that requires initial and continuous attention to securing airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies, including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. Lumbar puncture, comprehensive toxicologic screens, MRI, and other laboratory tests are performed depending on clinical suspicion and need. EEG is helpful in ruling out **pseudo–status epilepticus** (psychologic conversion reaction mimicking status epilepticus) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/de corticate posturing. The EEG can also be helpful in identifying the type of status epilepticus (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of status epilepticus in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation), and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology. The EEG manifestations of status epilepticus show several stages that consist of initial distinct electrographic seizures (stage I) followed by waxing and waning electrographic seizures (stage II), continuous electrographic seizures (stage III; many patients start with this directly), continuous ictal discharges punctuated by flat periods (stage IV), and periodic epileptiform discharges on flat background (stage V). The last 2 stages are often associated with subtle clinical manifestations and with a lower chance of response to medications.

The initial emergent therapy usually involves intravenous diazepam, lorazepam, or midazolam. Diazepam is at least as effective as intravenous lorazepam but has fewer side effects (Table 593-18). The use of midazolam autoinjector as initial therapy for acute seizures was found to be at least as useful and safe as the use intravenous lorazepam and results in earlier response. If intravenous access is not available, buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam are effective options. Intramuscular midazolam is equally effective as intravenous lorazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. In some infants, a trial of pyridoxine may be warranted. The strongest evidence for initial and emergent therapy is for diazepam or

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<tr>
<th>Table 593-18</th>
<th>Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus</th>
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<td><strong>DRUG</strong></td>
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<td>Topiramate</td>
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*Reflects current trends in use which may not be FDA approved. For FDA indications, see Table 593-13.

May cause PR prolongation.

PE, phenytoin sodium equivalents.
lorazepam, followed by phenytoin/fosphenytoin and phenobarbital, then valproate and levetiracetam.

After the emergent therapy usually with a benzodiazepine, the subsequent urgent therapy medication is usually fosphenytoin, and the loading dose is usually 15-20 PE/kg. A level is usually taken 2 hr later to ensure achievement of a therapeutic concentration. Depending on the level, maintenance dose can be started right away or, more commonly, in 6 hr. With phenytoin and phenobarbital, each 1 mg/kg (1 PE/kg for fosphenytoin) increases the serum concentration by approximately 1 µg/mL; for valproate, each 1 mg/kg increases the serum concentration by approximately 4 µg/mL. Precautions about the rate of infusion of fosphenytoin and phenytoin (not >0.5-1.0 mg/kg/min) and the other medications need to be followed because side effects often depend on infusion rate. The subsequent medication is often phenobarbital. The dose used in neonates is usually 20 mg/kg loading dose, but in infants and children the dose is often 5-10 mg/kg (to avoid respiratory depression), with the dose repeated if there is not an adequate response. Current evidence for the urgent therapy is strongest for valproate, followed by phenytoin/fosphenytoin and midazolam continuous infusion, followed by phenobarbital and levetiracetam, the last of which are currently being increasingly used.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with status epilepticus, even the ones who respond, need to be admitted to the ICU for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 min so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For refractory status epilepticus treatment, an intravenous bolus followed by continuous infusion of midazolam, propofol, phenobarbital, or thiopental is used. This is done in the ICU. Subsequent boluses and adjustment of the rate of the infusion are usually made depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to follow them. The goal is to stop electrographic seizure activity before reducing the therapy. 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Bibliography
Bibliography
Nodding Syndrome appears to be an epidemic progressive epilepsy encephalopathy syndrome of unknown etiology seen predominantly in Uganda, Liberia, Tanzania, and the southern Sudan, with a prevalence of approximately 6.8 per 1,000 children. Age of onset is 6-13 yr.

Nodding episodes are characterized by at least daily, rapid, paroxysmal forward head bobbing spells lasting several minutes; some patients are unresponsive whereas others may respond to commands or continue what they were doing before the episode. Children were previously healthy, although there may be a family history of seizures. In addition to episodes of nodding, there may be associated definable generalized tonic–clonic or absence seizures. Furthermore, patients go on to demonstrate severe and global cognitive impairment (see Table 593-19 for case definitions).

The EEG demonstrates a disorganized slow background and interictal generalized 2.5-3.0 Hz spike and slow waves. During a nodding episode, the EEG demonstrates generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. Cerebral spinal fluid analysis is usually negative, while the MRI shows cerebral and cerebellar atrophy.

Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperature may also trigger a nodding episode.

Treatment of seizures are indicated; however, the response to treatment is poor.

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


The misdiagnosis of epilepsy is estimated to be as high as 5-40%, implying that many patients may be subjected to unnecessary therapy and tests. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough exam; but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones and other devices at home or at school can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age of presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other abnormal movements and postures, (3) oculomotor abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 594-1).

**SYNCOPE AND OTHER GENERALIZED PAROXYSMS**

**Apnea**

Apneic episodes in neonates are usually associated with bradycardia as is usually apnea resulting from brainstem compression. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Of note, exceptions do occur as bradycardia can occur during epileptic seizures, and severe apnea of any cause can be followed by anoxic seizures.
Part XXVII  The Nervous System

Breath-Holding Spells
The term breath-holding spells is actually a misnomer, as these are not self-induced, but result from the immaturity of the autonomic system and occur in 2 different forms. The first type is the pallid breath-holding spell, which is caused by reflex vagal–cardiac bradycardia and asystole. The second type is the cyanotic, or “blue,” breath-holding spell, which does not occur during inspiration, but results from prolonged expiratory apnea and intrapulmonary shunting. Episodes usually start with a cry (often, in the case of the pallid type, a “silent” cry with marked pallor), and progress to apnea and cyanosis. Spells usually begin between 6 and 18 mo of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more-severe episodes, particularly in breath-holding spells of the pallid type. Injury, anger, and frustration, particularly with surprise, are common triggers. Education and reassurance of the parents is usually all that is needed, as these episodes are, as a rule, self-limited and are outgrown within a few years. However, treatment of coexisting iron deficiency is needed if it is present as the spells are made worse by iron-deficiency anemia. Anticholinergic drugs (e.g., atropine sulfate 0.01 mg/kg/24 hr in divided doses with a maximum daily dose of 0.4 mg), or antiepileptic drug therapy for coexisting anoxic seizures that are recurrent and not responding to other measures may, rarely, be needed. It is important all patients with syncope and can sometimes be manifestations of complex partial seizures such as ral lobe epilepsy, occurs in vasovagal syncope, and can be a trigger or other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope, and can be a trigger or a consequence of that process (intestinal vagal discharge). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remission. Some clinicians advocate the use of naloxone in such cases.

Neurally Mediated Syncope
Syncope can present with drop attacks and can also lead to generalized convulsions, termed anoxic seizures. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to and can be misdiagnosed as generalized epileptic seizures. Vasovagal (neu rocardiogenic) syncope is one of the most common mimickers of generalized tonic–clonic seizures and is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, and or sudden stress. History is usually the clue to distinguishing syncope from epileptic seizures: There is initially pallor and sweating followed by blurring of vision, dizziness, nausea, and then gradual collapse with loss of consciousness. These symptoms are present in most, although not necessarily all patients with syncope and can sometimes be manifestations of complex partial seizures. Much more important is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However when they precede an epileptic convulsion, such features usually start suddenly are short in duration, paroxysmal and are followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope, and can be a trigger or a consequence of that process (intestinal vagal discharge). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected 1st-degree relative; reports demonstrate

Compulsive Valsalva
In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers like Valsalva. In this case, true breath-holding occurs, and it usually lasts for approximately 10 sec during inspiration. Some clinicians advocate the use of naloxone in such cases.

Table 594-1  Conditions That Mimic Seizures According to Age of Presentation

<table>
<thead>
<tr>
<th>AGE</th>
<th>SYNOCOPE AND OTHER GENERALIZED PAROXYSMS</th>
<th>MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS</th>
<th>OCULOMOTOR ABNORMALITIES</th>
<th>SLEEP DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>Apnea</td>
<td>Jitteriness</td>
<td>Paroxysmal tonic upgaze</td>
<td>Paroxymal tonic upgaze</td>
</tr>
<tr>
<td></td>
<td>Apnea</td>
<td>Hyperkplexia</td>
<td>Alternating hemiplegia</td>
<td>Alternating hemiplegia of childhood</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal extreme pain disorder</td>
<td>Paroxysmal dystonic choreoathetosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>Reflex anoxic seizures</td>
<td>Jitteriness</td>
<td>Paroxomalous tonic upgaze</td>
<td>Paroxomalous tonic upgaze</td>
</tr>
<tr>
<td></td>
<td>Breath-holding spells</td>
<td>Sandifer</td>
<td>Oculomotor apraxia</td>
<td>Oculomotor apraxia</td>
</tr>
<tr>
<td></td>
<td>Benign paroxysmal vertigo</td>
<td>Paroxysmal dystonic choreoathetosis</td>
<td>Spasmus nutans</td>
<td>Spasmus nutans</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal extreme pain disorder</td>
<td>Benign myoclonus of early infancy</td>
<td>Opsoclonus myoclonus</td>
<td>Opsoclonus myoclonus syndrome</td>
</tr>
<tr>
<td>Children and adolescents</td>
<td>Benign paroxysmal vertigo</td>
<td>Tics</td>
<td>Daydreaming</td>
<td>Non-REM partial- arousal disorders</td>
</tr>
<tr>
<td></td>
<td>Compulsive Valsalva</td>
<td>Tremor</td>
<td>Drug reactions</td>
<td>Non-REM partial- arousal disorders</td>
</tr>
<tr>
<td></td>
<td>Familial hemiplegic migraine</td>
<td>Pathologic startle</td>
<td></td>
<td>REM sleep disorders</td>
</tr>
<tr>
<td></td>
<td>Syncope (long QT, vasovagal, vagovagal,</td>
<td>Paroxysmal dyskinesias</td>
<td></td>
<td>Sleep transition disorders</td>
</tr>
<tr>
<td></td>
<td>orthostatic, migraine induced)</td>
<td>Alternating hemiplegia of childhood</td>
<td></td>
<td>(somnambulism, somniloquy)</td>
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<tr>
<td></td>
<td>Psychogenic seizures</td>
<td>Benign paroxysomal tetocolis</td>
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<td>Sleep myoclonus</td>
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<tr>
<td></td>
<td>Transient global amnesia</td>
<td>Episodic ataxia</td>
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<td>Restless legs syndrome</td>
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<tr>
<td></td>
<td>Hyperventilation spells</td>
<td>Psychologic disorders including factitious</td>
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<td></td>
<td></td>
<td>disorder imposed on another, malingering</td>
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<td></td>
<td></td>
<td>Masturbation</td>
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<td></td>
<td></td>
<td>Psychogenic seizures</td>
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<td></td>
<td></td>
<td>Cataplex</td>
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<td></td>
<td></td>
<td>Jactatio capitis (head banging)</td>
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<tr>
<td></td>
<td></td>
<td>Episodic rage</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Drug reactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REM, rapid eye movement.


REM, rapid eye movement.
autosomal dominant inheritance at least in some families. The EEG is normal and the tilt test has been used for diagnostic purposes in selected cases. In most cases with typical history, this test is not needed. Vagovagal syncope can progress to convulsive seizure if the asystole is sufficiently prolonged. Sudden cold exposure to the face or to the body can also trigger vagal syncope. Syncope has been reported (rarely) to occur in association with cough, tight hair braiding, and hair combing. Orthostatic hypotension and orthostatic intolerance manifest symptoms that develop during upright standing and can be relieved by recumbence. Postural tachycardia syndrome, the pathophysiology of which presumably involves an excessive sympathetic discharge resulting in increased heart rate and vasoconstriction that can lead to decreased peripheral perfusion, is usually a disease of adolescent females that is characterized by upright syncope/near syncope, and tachycardia with normal or even increased blood pressure during the episode. Primary autonomic failure is rare in children, and familial dysautonomia is the only relatively common form. Familial dysautonomia is a disease common in Ashkenazi Jews and is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction following intradermal histamine. Dopamine β-hydroxylase deficiency is a very rare cause of primary autonomic failure, and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, impaired ejaculation, and nocturia. The tilt test causes a drop in both blood pressure and heart rate in patients with classic vasovagal syncope. It results in a blood pressure drop with minimal change in heart rate in autonomic failure, and in blood pressure drop and an increase in heart rate in postural tachycardia syndrome. Management of syncope centers on avoidance of precipitating factors (maintenance of hydration, avoidance of standing still, rising slowly from sitting, first-aid measures, raising of the legs, positioning) and treatment of any accompanying or underlying medical conditions (anemia, adrenal insufficiency, cardiac, etc.). In addition, salt supplementation (2-4 g/day), β-blockers (e.g., metoprolol at a starting dose of 1-2 mg/kg once per day up to a maximum of 6 mg/kg/day), or fluoroxydrol for (0.05-0.1 mg/day) therapy may be needed in selected cases. Cardiac Syncope See Chapter 435.5.

Long QT syndromes (LQT) can cause life-threatening “pallid” or white syncope. Accompanying this are ventricular arrhythmias, usually torsades de pointes or even ventricular fibrillation. There are more than 10 types of prolonged QT syndrome. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and Lange-Nielson syndrome (type 1, LQT 1, associated with KVLQT1 potassium channel mutation). The Romano-Ward syndrome is an autosomal dominant syndrome with incomplete penetrance that is caused by a potassium channel mutation). LQT 3 is associated with an SCN1A sodium channel subunit mutation, LQT 4 with ankyrin protein mutation, LQT 5 (milder form) with KCNE1 mutations, LQT 6 with KCNE2 potassium gene mutation, LQT 7 with cavin sodium channel-related protein mutations, and LQT 10 with SCN4B sodium channel mutations. LQT 7 and LQT 8 are of particular interest because of associated clinical and neurologic manifestations. LQT 7 (Andersen-Tawil) syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (mutations in KCNJ2 gene). LQT 8 or the Timothy syndrome (mutations in the calcium channel gene CACNA1c) manifests congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected LQT syndrome individual should be investigated. Affected individuals need insertion of cardiac defibrillators, and their families should be taught CPR. As a rule, children with new-onset seizure disorder should get an electrocardiogram to rule out LQT syndrome masquerading as seizure disorder. Cardiac syncope is usually sudden without the gradual onset and the symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of the exercise (usually hyperventilating), or directly at the end (usually valvular) and, if suspected, warrants an echocardiogram.

Other Causes of Syncope

Syncope that is not neurally mediated or cardiac in origin is caused by a decrease in blood volume, or a mechanical disruption of brain perfusion. Systemic diseases that lead to syncope by affecting blood volume (e.g., adrenal insufficiency) are usually first brought to medical attention by other accompanying signs and symptoms. In stretch syncope, which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward, or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some cases, this may be associated with an abnormally prolonged stylomastoid process compressing the carotids. If the latter condition is suspected, then neuroimaging (CT, MRI) is required for proper diagnosis of the stylo-mastoid anomaly.

Sporadic and Familial Hemiplegic Migraine

This is a rare type of migraine with a motor aura of weakness. Attacks begin as early as 5-7 yr of age. In a genetically susceptible person, attacks may be precipitated by head trauma, exertion, or emotional stress. The gap genes so far identified are SCN1A (neuronal sodium channel subunit), CACNA1A (neuronal calcium channel subunit), and ATP1A2 (sodium potassium adenosine triphosphatase subunit). However at least a quarter of the affected families, and most of the sporadic cases do not carry a mutations in these 3 genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights), and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks and verapamil and ketamine have been used for the acute episode, while ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patients with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like episodes).

Benign Paroxysmal Vertigo of Childhood

This is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that is often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubant) where children sometimes report that objects are moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 yr of age. MRI and EEG are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydrine, 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may be rarely needed for frequent attacks.

Cyclic Vomiting Syndrome

This syndrome is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. This and other periodic syndromes have been associated with mutations that also can cause hemiplegic migraine.

The “Alice in Wonderland” Syndrome

This is the episodic experience of transient distortions of body image or visual images that, most often, constitute a migraine equivalent. It also can be an epileptic phenomenon.
Migraine-Induced Syncope
Migraine, usually of the basilar variety, can trigger vasovagal syncope and, less commonly, epileptic seizures. Careful elicitation of the history of a migrainous prelude to the syncope helps in identifying these phenomena.

Psychogenic Disorders
Psychogenic nonepileptic seizures are conversion reactions that are usually suspected clinically based on the characteristics of the spells (Table 594-2). The diagnosis can be confirmed by video EEG with capture of an episode to eliminate any residual doubts about their nature, as they can often occur in patients who also have epileptic seizures. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes. Psychiatric evaluation and follow-up are needed to uncover underlying psychopathology, and to establish continued support as psychogenic seizures can persist over long periods of time. Malingering and factitious disorder imposed on another (formerly called Munchausen syndrome by proxy) are often difficult to diagnose but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful.

Paroxysmal Extreme Pain Disorder
Paroxysmal extreme pain disorder was previously called familial rectal pain syndrome. This syndrome (caused by the SCN9A sodium channel gene mutation) usually starts in the neonatal period or infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole are common. Later, the disorder is characterized by attacks of excruciating deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defeca-

tion, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Gain-of-function \( \text{Na}(v)1.7 \) mutations are known to cause two neuropathic pain syndromes: inherited erythromelalgia and paroxysmal extreme pain syndrome. These syndromes are inherited in a dominant trait; they usually begin in childhood or infancy, and are characterized by attacks of severe neuropathic pain accompanied with autonomic symptoms. In addition, small fiber neuropathy and chronic nonparoxysmal pain have been described in patients harboring gain-of-function mutations in \( \text{Na}(v)1.7 \) channel. Loss-of-function mutations in \( \text{Na}(v)1.7 \) are extremely rare and invariably cause congenital inability to perceive pain.

Autonomic Storms (Diencephalic Seizures)
Spells of hyperhidrosis, changes in blood pressure, temperature and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term \textit{diencephalic seizures} is discouraged as these are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, anticonvulsants, cyproheptadine, morphine, and sympathectomy. Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs like St. John’s Wort and some other medications can produce similar symptoms, and if not recognized, can at times be fatal as can be the similar neuroleptic malignant syndrome caused by antipsychotic medications.

MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS AND POSTURES

Neonatal Jitteriness and Clonus
Jitteriness consists of equal backward and forward movements of limbs, occurring spontaneously, or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the 2-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks, point to a nonepileptic event.

### Table 594-2
Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)</th>
<th>PRODROME</th>
<th>ICTAL SYMPTOMS</th>
<th>POSTICTAL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized seizures</td>
<td>Sleep deprivation, television, video games, visual patterns, and photic stimulation</td>
<td>Rarely irritability or nonspecific behavioral changes</td>
<td>Usually 2-3 min Consciousness might be preserved if atonic, or in some, tonic seizures</td>
<td>Delayed recovery with postictal depression, incontinence (may be ictal also)</td>
</tr>
<tr>
<td>Syncope: vasovagal</td>
<td>Fatigue, emotional stress, dehydration, vomiting, choking, swallowing</td>
<td>Blurring of vision, tinnitus, dizziness Crying in breath-holding spells</td>
<td>Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures</td>
<td>Rapid recovery with no postictal depression</td>
</tr>
<tr>
<td>Syncope with reflex anoxic seizures</td>
<td>Minor bump to head, upsetting surprises</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope: trigeminal vagal</td>
<td>Standing up, bathing, awakening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope: orthostatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperekplexia</td>
<td>Auditory and tactile stimuli</td>
<td>None</td>
<td>Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles</td>
<td>Depending on severity, may have postictal depression</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Exercise</td>
<td>None</td>
<td>Loss of consciousness, often only few seconds, pallor</td>
<td>Rarely</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Suggestion, stress</td>
<td>None</td>
<td>Eyes closed Asynchronous flailing limb movements that vary between attacks</td>
<td>No postictal depression</td>
</tr>
</tbody>
</table>

Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic–ischemic encephalopathy are possible etiologies. Clonus as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by change in position.

**Hyperkplexia (Stiff Baby Syndrome) and Pathologic Startles**

Hyperkplexia is a rare, sporadic or dominantly inherited disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures. Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 yr of age and may disappear during sleep.

The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important to initiate treatment with clonazepam as hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes.

In other children after brain injury, and in many patients with cerebral palsy, an exaggerated startle reflex can occur. This is more common than hyperkplexia. In Tay-Sachs disease and similar gangliosidoses, exaggerated startle to sound occurs and has been, inappropriately, interpreted as hyperacusis. In Tay-Sachs disease and similar gangliosidoses, exaggerated startle to sound occurs and has been, inappropriately, interpreted as hyperacusis.

**Benign Paroxysmal Torticollis of Infancy**

This condition typically presents as morning episodes of painless retrocollis, and later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements, and progress to stillness in an abnormal posture. This usually lasts for minutes or hours and, at times, days. Neurologic exam between attacks, EEG, and neuromaging are normal. It affects girls more than boys (3:1) and may manifest before 3 mo of age, and spontaneously remits before the age of 5 yr. Medical therapy is not needed. It is considered to be a migraine equivalent and cosegregates with migraine in families.

**Sandifer Syndrome**

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodic movements often occur 30 min after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of latero-, retro-, or torticollis, the exact pathophysiology of which remains elusive.

**Alternating Hemiplegia of Childhood**

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting 1 or both sides lasting minutes to days, starting in the 1st 18 mo of life. Early manifestations include paroxysmalystagmus, which is often monocular and ipsilateral to the hemiplegia. Dystonic and tonic spells often occur and can be confused with seizures and the hemiplegia with Todd paralysis. Attacks can be triggered by bathing, cold, fatigue, hyperthermia, and emotional stress, and they remit during sleep and for about 15 minutes or so after waking up. Most cases are caused by mutations in the ATP1A3 gene while, rarely, a similar clinical picture can occur as a result of mutations in ATP1A2 or in the glucose transporter 1 (GLUT1/SLC2A1) gene mutations. Flu-narazine 2.5-15 mg/day reduces the frequency of the attacks. Most children ultimately develop ataxia, developmental delay, and persistent choreoathetosis.

**Paroxysmal Dyskinesias and Other Movement Disorders**

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 594-3). A sensation of fatigue or weakness confined to 1 side may herald an attack. Consciousness is preserved and patients may be able perform a motor activity, like walking, despite the attack. The variability in the pattern of severity and localizations among different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence, and steadily decreases in the 3rd decade. Neurologic exam between attacks, EEG, laboratory investigations, and imaging studies are normal. These dyskinesias often respond to phenytoin, carbamazepine, clonazepam, or to antidopaminergic drugs such as haloperidol. Drug reactions can result in abnormal movements such as oculogyric crisis with many antiemetics, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Mutations of the glucose transporter 1 (GLUT1/SLC2A1) gene have been described in patients with exercise-induced dyskinesia.

**Motor Tics**

These are movements that are under partial control, and are associated with an urge to do them and with a subsequent relief. They are usually exacerbated by emotions, and often change in character over time. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive compulsive disorder or personality traits.

**Episodic Ataxias**

Episodic ataxia encompasses 7 clinically and genetically heterogeneous syndromes, only 2 of which (types 1 and 2) have been described in a large number of families. Type 1 is caused by mutations in the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia, and occasional partial seizures with interictal myokymia as a main diagnostic feature. Type 2 is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by mutations in the voltage-gated calcium channel gene CACNA1A. This type is more responsive than type 1 to acetazolamide that reduces the frequency and severity of attacks, but not the interictal signs and symptoms.

**Benign Myoclonus of Early Infancy, Shuddering Attacks, and Chin Trembling**

Benign myoclonus consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep. It has been suggested by some that these attacks are in the same spectrum as shuddering attacks. Shuddering attacks are characterized by rapid tremor of the head, shoulder, and trunk, lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor as family history of essential tremor is often present. The clinical events in either of these can be mistaken for infantile spasms, but ictal and interictal EEG, MRI, and development are normal. Spontaneous remission occurs in both usually within a few months. Hereditary chin trembling at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

A novel type of non epileptic attack with infantile onset characterized in 3 patients as clusters of repeated head drops, mimicking epileptic negative myoclonus of the neck, accompanied by crying. The episodes occurred for 5 or 6 mo and disappeared by the end of the 1st yr. Language and cognition were normal. This is a different form of myoclonic activity that may complicate the diagnosis of infantile spasms and West syndrome; thorough EEG investigation is needed in such cases.

**Brainstem Dysfunction**

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus,
hemorrhage, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. In addition, crowding of the posterior fossa and near herniation, the so-called cerebellar fits can also lead to abnormal extensor posturing, drop attacks, and varying degrees of altered consciousness and respiratory compromise. Historically secondary to undiagnosed posterior fossa tumors in the preneuroimaging era, “cerebellar fits” mostly occur in the context of Chiari I malformations.

Psychologic Disorders

Many psychologic disorders can be mistaken for epileptic seizures. Pleasurable behavior similar to masturbation may occur from infancy onward, and may result of rhythmic rocking movement in a sitting or lying position, or rhythmic hip flexion and adduction. Masturbation may occur in girls 2-3 yr of age and is often associated with perspiration, irregular breathing, and grunting, but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. Stereotypies, or repetitive movements that are more complex than tics and do not change and wax and wane like tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. A mannerism is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies which are generally pervasive over almost every other activity such as head-shaking or hand-flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 yr, involve more body parts, are more rhythmic and most importantly occur with engagement with an object or activity of interest and do not have a premonitory urge that increases with attempts to suppress them as children rarely try to suppress stereotypies. Panic and anxiety attacks have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures, and therefore may necessitate video-EEG monitoring. Rage attacks usually occur in patients with personality disorder and are usually not seizures although rare cases of partial seizures can manifest as rage attacks. Hyperventilation spells can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. Transient global amnesia consists of isolated short-term memory loss for minutes to hours that occur mostly in the elderly. The etiology can be epileptic, vascular, or drug related.

**Oculomotor Abnormalities and Visual Hallucinations**

**Paroxysmal Tonic Upgaze of Childhood**

This usually starts before 3 mo of age, and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Imaging, laboratory, and neuropsychologic examinations are usually nonrevealing. Therapy with low-dose levodopa/carbidopa may be helpful.

**Oculomotor Apraxia and Saccadic Intrusions**

In oculomotor apraxia saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan oculomotor apraxia) or may occur in the context of ataxia telangiectasia or lysosomal storage diseases. Genetic defects in DNA repair mechanisms have been implicated in at least 4 spinocerebellar ataxia disorders that are accompanied by oculomotor apraxia. A selective loss of Purkinje cells required to inhibit gaze saccades is seen in ataxia telangiectasia. Saccades are necessary for horizontal gaze deviation, and, therefore, may result of a disconnection between the brainstem motor network, and the frontal cortex. In addition, crowding of the posterior fossa and near herniation, the so-called cerebellar fits can also lead to abnormal extensor posturing, drop attacks, and varying degrees of altered consciousness and respiratory compromise. Historically secondary to undiagnosed posterior fossa tumors in the preneuroimaging era, “cerebellar fits” mostly occur in the context of Chiari I malformations.

**Spasmus Nutans**

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like epileptic seizures. Brain MRI should be performed, as the triad has been
associated with masses in the optic chiasm and third ventricle. Retinal
disease should also be ruled out. In the absence of these associations,
remission occurs before 5 yr of age.

**Opsoclonus Myoclonus Syndrome**
The so-called dancing eyes refers to continuous, random, irregular, and
conjugate eye movements that may fluctuate in intensity. They usually
accompany myoclonus and ataxia (“dancing feet”). Encephalitis and
neuroblastoma are possible causes. Therapy is by treating the underly-
ing etiology, but adrenocorticotropic hormone (ACTH), corticoste-
oroids, and clonazepam may be needed. Rituximab has been studied and
preliminary trials suggest it may be effective as well.

**Daydreaming and Behavioral Staring**
Staring may be a manifestation of absence seizures, which should be
differentiated from daydreaming, behavioral staring because of fatigue,
and inattention. Episodes of staring only in certain settings (e.g.,
school) are unlikely to be seizures. In addition, responsiveness to stim-
ulation such as touch and lack of interruption of playing activity char-
acterizes nonepileptic staring.

**Visual Hallucinations**
Visual perceptions in the absence of external stimuli, or visual hallu-
cinations, are usually accompanied by other neurologic signs and
symptoms when they occur in the context of seizures. An exception is
occipital seizures, which can manifest with isolated and unformed
visual hallucinations and may be accompanied by headache and
nausea, making them difficult to differentiate from migraine. However,
occipital seizures are characterized by colorful, shapes, circles and
spots lasting seconds and confined to 1 hemifield, while migraineous
auras usually last minutes, and consist of black-and-white lines, scoto-
mas, and or fortification spectra that start in the center of vision. Hal-
lucinations can also be secondary to drug exposure, midbrain lesions,
and psychiatric illnesses. In addition, retinal-associated hallucinations
can occur in the form of flashes of light in the context of inflammatory
etiologies, trauma, or optic nerve edema.

**SLEEP DISORDERS**
Paroxysmal nonepileptic sleep events are more common in epileptic
patients than in the general population, which makes their diagnosis
difficult. Semiology, timing of events, and if needed video-EEG and
polysomnography help in distinguishing epileptic from nonepileptic
events. Parasomnias typically occur less than once or twice a night;
more frequent episodes suggest epileptic seizures. Of note, the EEG
pattern of frontal lobe epileptic seizures may be similar to the one seen
in a normal arousals, making their diagnosis challenging, especially
that they have nonspecific hypermotor manifestations such as thrash-
ing, body rocking, kicking, boxing, pedaling, bending, running, and
various vocalizations. The diagnosis of such epileptic seizures is made
on the basis of highly stereotyped events arising several times a night
from nonrapid eye movement sleep.

**Benign Sleep Myoclonus and
Neonatal Sleep Myoclonus**
Neonatal sleep myoclonus consists of repetitive, usually bilateral rhyth-
mic jerks involving the upper and lower limbs during nonrapid eye
movement sleep, sometimes mimicking clonic seizures. A slow (1 Hz)
rocking of the infant in a head-to-toe direction is a specific diagnostic
test that may reproduce the myoclonus. The lack of autonomic changes,
occurrence only in sleep, and suppression by awakenings may help in
differentiating these events from epileptic seizures. Remission is spont-
aneous at 2-3 mo of age. In older children and adults, sleep myoclonus
consists of random myoclonic jerks of the limbs.

**Nonrapid Eye Movement Partial
Arousal Disorders**
Brief nocturnal confusional arousals occurring 1-2 hr after sleep in
stage 4 sleep are normal in children. Such episodes can vary from
chewing, sitting up, and mumbling to agitated sleep walking, and
usually last for 10-15 min. Night terrors similarly occur a few hours
after going to sleep in stage 3 or 4 of sleep, most often at 2-7 yr of age
and more so in boys. The child screams; appears terrified; has dilated
pupils, tachycardia, tachypnea, unresponsiveness, agitation, and
thrashing that increase with attempts to be consoled; is difficult to
arouse; and may have little or no vocalization. In older children with
persistent night terrors, an underlying psychologic etiology may be
present. Diagnosis is based on the history. However, rarely, video EEG
monitoring may be needed. At times, the use of bedtime diazepam
(0.2-0.3 mg/kg) or clonazepam (0.01 mg/kg) may help control the
problem while psychologic factors are being investigated. Restless leg
syndrome can cause painful leg dysesthesias that cause nocturnal
arousals and insomnia. It can be either genetic or associated with iron
deficiency, systemic illness, or some drugs. Therapy depends upon
treating the underlying cause and, if needed, on dopaminergic drugs
such as levodopa/carbidopa, or antiepileptics like gabapentin.

**Rapid Eye Movement Sleep Disorders**
Nightmares and sleep paralysis are common disorders. Unlike night
terrors, nightmares tend to occur later during the night and the child
has a memory of the event.

**Sleep Transition Disorders**
Nocturnal head banging (jactatio capitis nocturna), rolling, or body
rocking often occurs in infants and toddlers as they are trying to fall
asleep. These usually remit spontaneously by 5 yr of age. No specific
therapy is needed.

**Narcolepsy-Cataplexy Syndrome**
Narcolepsy is characterized by excessive daytime sleepiness, cataplexy,
sleep paralysis, hypnagogic hallucinations, and disturbed nighttime
sleep. The persistence of rapid eye movement sleep atonia upon awak-
ening or its intrusion during wakefulness lead to sleep paralysis or
cataplexy, respectively. Loss of tone in cataplexy occurs in response to
strong emotions, and spreads from the face downwards leading to a
fall in a series of stages rather than a sudden one. Consciousness is
maintained in cataplexy. A selective loss of hypocretin-secreting
neurons in the hypothalamus is at the origin of this disorder. The fact
that DQB1*0602 is a predisposing HLA allele identified in 85-95% of
patients with narcolepsy-cataplexy suggests an autoimmune-mediated
neuronal loss. Diagnosis is based on the multiple sleep latency test,
and therapy relies on scheduled naps, amphetamines, methylpheni-
date, tricyclic antidepressants, and counseling about precautions in
work and driving.

*Bibliography is available at Expert Consult.*
Bibliography
Headache is a common complaint in children and adolescents. Headaches can be a primary problem or occur as a symptom of another disorder, representing a secondary problem. Recognizing this difference is essential for choosing the appropriate evaluation and treatment to ensure successful management of the headache. Primary headaches are most often recurrent, episodic headaches and for most children are sporadic in their presentation.

The most common forms of primary headache of childhood are migraine and tension-type headaches (Table 595-1). Other forms of
### Part XXVII  ●  The Nervous System

#### Table 595-1  Classification of Headaches (ICHD-3 Beta Code Diagnosis)

<table>
<thead>
<tr>
<th>MIGRAINE</th>
<th>HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine with or without aura</td>
<td>Headache attributed to ischemic stroke or transient ischemic attack</td>
</tr>
<tr>
<td>Migraine with typical aura (with or without headache)</td>
<td>Headache attributed to nontraumatic intracerebral hemorrhage</td>
</tr>
<tr>
<td>Migraine with brainstem aura</td>
<td>Headache attributed to nontraumatic subarachnoid hemorrhage (SAH)</td>
</tr>
<tr>
<td>Hemiplegic migraine (sporadic or familial types 1, 2, 3, or other genetic loci)</td>
<td>Headache attributed to nontraumatic acute subdural hemorrhage (ASDH)</td>
</tr>
<tr>
<td>Retinal migraine</td>
<td>Headache attributed to unruptured vascular malformation</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>Headache attributed to unruptured saccular aneurysm</td>
</tr>
<tr>
<td>Complications of Migraine</td>
<td>Headache attributed to arteriovenous malformation (AVM)</td>
</tr>
<tr>
<td>Status migrainous</td>
<td>Headache attributed to dural arteriovenous fistula (DAVF)</td>
</tr>
<tr>
<td>Persistent aura without infarction</td>
<td>Headache attributed to cavernous angioma</td>
</tr>
<tr>
<td>Migrainous infarction</td>
<td>Headache attributed to encephalotrigenial or leptomeningeal angiomatosis (Sturge-Weber syndrome)</td>
</tr>
<tr>
<td>Migraine aura-triggered seizure</td>
<td>Headache attributed to arteritis</td>
</tr>
<tr>
<td>Episodic Syndromes That May Be Associated with Migraine</td>
<td>Headache attributed to giant cell arteritis (GCA)</td>
</tr>
<tr>
<td>Recurrent gastrointestinal disturbance</td>
<td>Headache attributed to primary angitis of the central nervous system (PACNS)</td>
</tr>
<tr>
<td>Cyclic vomiting syndrome</td>
<td>Headache attributed to secondary angitis of the central nervous system (SACNS)</td>
</tr>
<tr>
<td>Abdominal migraine</td>
<td>Headache attributed to cervical carotid or vertebral artery disorder</td>
</tr>
<tr>
<td>Benign paroxysmal vertigo</td>
<td>Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection</td>
</tr>
<tr>
<td>Benign paroxysmal torticollis</td>
<td>Post-endarterectomy headache</td>
</tr>
<tr>
<td>TENSION-TYPE HEADACHE (TTH)</td>
<td>Headache attributed to carotid or vertebral angioplasty</td>
</tr>
<tr>
<td>Infrequent episodic tension-type headache associated with or without pericranial tenderness</td>
<td>Headache attributed to cerebral venous thrombosis (CVT)</td>
</tr>
<tr>
<td>Frequent episodic tension-type headache associated with or without pericranial tenderness</td>
<td>Headache attributed to other acute intracranial arterial disorder</td>
</tr>
<tr>
<td>Chronic tension-type headache associated with or without pericranial tenderness</td>
<td>Headache attributed to an intracranial endovascular procedure</td>
</tr>
<tr>
<td>Probable tension-type headaches</td>
<td>Angiography headache</td>
</tr>
<tr>
<td>TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)</td>
<td>Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)</td>
</tr>
<tr>
<td>Cluster headache (episodic or cluster)</td>
<td>Headache attributed to intracranial arterial dissection</td>
</tr>
<tr>
<td>Paroxysmal hemicrania (episodic or cluster)</td>
<td>Headache attributed to genetic vasculopathy</td>
</tr>
<tr>
<td>Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)</td>
<td>Cerebrovascular dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)</td>
</tr>
<tr>
<td>Episodic SUNCT</td>
<td>Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)</td>
</tr>
<tr>
<td>Chronic SUNCT</td>
<td>Headache attributed to another genetic vasculopathy</td>
</tr>
<tr>
<td>Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)</td>
<td>Headache attributed to pituitary apoplexy</td>
</tr>
<tr>
<td>Episodic SUNA</td>
<td></td>
</tr>
<tr>
<td>Chronic SUNA</td>
<td></td>
</tr>
<tr>
<td>Hemicrania continua</td>
<td></td>
</tr>
<tr>
<td>Probable trigeminal autonomic cephalalgias</td>
<td></td>
</tr>
<tr>
<td>OTHER PRIMARY HEADACHE DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Primary cough headache</td>
<td>HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER</td>
</tr>
<tr>
<td>Primary exercise headache</td>
<td>Headache attributed to increased cerebrospinal fluid pressure</td>
</tr>
<tr>
<td>Primary headache associated with sexual activity</td>
<td>Headache attributed to idiopathic intracranial hypertension (IH)</td>
</tr>
<tr>
<td>Primary thunderclap headache</td>
<td>Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes</td>
</tr>
<tr>
<td>Cold-stimulus headache (external application, ingestion, or inhalation)</td>
<td>Headache attributed to intracranial hypertension secondary to hydrocephalus</td>
</tr>
<tr>
<td>External-pressure headache</td>
<td>Headache attributed to low cerebrospinal fluid pressure</td>
</tr>
<tr>
<td>External-compression headache</td>
<td>Headache attributed to postural puncture headache</td>
</tr>
<tr>
<td>External-traction headache</td>
<td>Cerebrospinal fluid fistula headache</td>
</tr>
<tr>
<td>Primary stabbing headache</td>
<td>Headache attributed to spontaneous intracranial hypotension</td>
</tr>
<tr>
<td>Nummular headache</td>
<td>Headache attributed to noninfectious inflammatory disease</td>
</tr>
<tr>
<td>Hyponic headache</td>
<td>Headache attributed to neurosarcoidosis</td>
</tr>
<tr>
<td>New daily persistent headache (NDPH)</td>
<td>Headache attributed to asptic (noninfectious) meningitis</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to other noninfectious inflammatory disease</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to lymphocytic hypophysitis</td>
</tr>
<tr>
<td></td>
<td>Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to intracranial neoplasm</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to colloid cyst of the third ventricle</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to carcinomatous meningitis</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to hypothalamic or pituitary hyper- or hyposecretion</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to intrathecal injection</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to epileptic seizure</td>
</tr>
<tr>
<td></td>
<td>Hemicrania episclerica</td>
</tr>
<tr>
<td></td>
<td>Postictal headache</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to Chiari malformation type I (CM1)</td>
</tr>
<tr>
<td></td>
<td>Headache attributed to other nonvascular intracranial disorder</td>
</tr>
</tbody>
</table>
primary headache, including the trigeminal autonomic cephalalgias, occur much less commonly. Primary headache can progress to very frequent or even daily headaches with chronic migraine and chronic tension-type headaches being increasingly recognized. These more frequent headaches can have an enormous impact on the life of the child and adolescent, as reflected in school absences and decreased school performance, social withdrawal, and changes in family interactions. To reduce this impact, a treatment strategy that incorporates acute treatments, preventive treatments, and biobehavioral therapies must be implemented.

Secondary headache involves headaches that are a symptom of an underlying illness (see Table 595-1). The underlying illness should be clearly present as a direct cause of the headaches. This is often difficult when 2 or more common conditions occur in close temporal association. This frequently leads to the misdiagnosis of a primary headache as a secondary headache. This is, for example, the case when migraine is misdiagnosed as a sinus headache. In general, the key components of a secondary headache are the likely direct cause-and-effect relationship between the headache and the precipitating condition, and the lower likelihood in a specific patient and circumstance of the headache being the result of a recurrent headache disorder. In addition, once the underlying suspected cause is treated, the secondary headache should resolve. If this does not occur, either the diagnosis must be reevaluated or the effectiveness of the treatment reassessed. One key clue that additional investigation is warranted is the presence of an abnormal neurologic examination or unusual neurologic symptoms.

### Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)—cont’d

<table>
<thead>
<tr>
<th>HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL</th>
<th>HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache attributed to use of or exposure to a substance</td>
<td>Headache attributed to disorder of cranial bone</td>
</tr>
<tr>
<td>Nicotine (NO) donor-induced headache</td>
<td>Headache attributed to retropharyngeal tendinitis</td>
</tr>
<tr>
<td>Phosphodiesterase (PDE) inhibitor-induced headache</td>
<td>Headache attributed to craniocervical dystonia</td>
</tr>
<tr>
<td>Carbon monoxide (CO)-induced headache</td>
<td>Headache attributed to acute glaucoma</td>
</tr>
<tr>
<td>Alcohol-induced headache</td>
<td>Headache attributed to refractive error</td>
</tr>
<tr>
<td>Monosodium glutamate (MSG)-induced headache</td>
<td>Headache attributed to heterophoria or heterotropia (latent or persistent squint)</td>
</tr>
<tr>
<td>Cocaine-induced headache</td>
<td>Headache attributed to ocular inflammatory disorder</td>
</tr>
<tr>
<td>Histamine-induced headache</td>
<td>Headache attributed to trachilis</td>
</tr>
<tr>
<td>Calcitonin gene-related peptide (CGRP)-induced headache</td>
<td>Headache attributed to disorder of the ears</td>
</tr>
<tr>
<td>Headache attributed to exogenous acute pressor agent</td>
<td>Headache attributed to acute or chronic or recurring rhinosinusitis</td>
</tr>
<tr>
<td>Headache attributed to occasional or long-term use of nonheadache medication</td>
<td>Headache attributed to temporomandibular disorder (TMD)</td>
</tr>
<tr>
<td>Headache attributed to exogenous hormone</td>
<td>Headache or facial pain attributed to inflammation of the stylohyoid ligament</td>
</tr>
<tr>
<td><strong>Medication-Overuse Headache (MOH)</strong></td>
<td>Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure</td>
</tr>
<tr>
<td>Ergotamine-overuse headache</td>
<td><strong>HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER</strong></td>
</tr>
<tr>
<td>Triptan-overuse headache</td>
<td>Headache attributed to somatization disorder</td>
</tr>
<tr>
<td>Simple analgesic-overuse headache</td>
<td>Headache attributed to psychogenic disorder</td>
</tr>
<tr>
<td>Paracetamol (acetaminophen)-overuse headache</td>
<td><strong>PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS</strong></td>
</tr>
<tr>
<td>Acetylsalicylic acid-overuse headache</td>
<td>Classical trigeminal neuralgia</td>
</tr>
<tr>
<td>Other non-steroidal antiinflammatory drug (NSAID)-overuse headache</td>
<td>Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent pain</td>
</tr>
<tr>
<td>Opioid-overuse headache</td>
<td>Painful trigeminal neuropathy</td>
</tr>
<tr>
<td>Combination analgesic-overuse headache</td>
<td>Painful trigeminal neuropathy attributed to acute herpes zoster</td>
</tr>
<tr>
<td><strong>Headache Attributed to Substance Withdrawal</strong></td>
<td>Postherpetic trigeminal neuropathy</td>
</tr>
<tr>
<td>Caffeine-withdrawal headache</td>
<td>Painful posttraumatic trigeminal neuropathy</td>
</tr>
<tr>
<td>Opioid-withdrawal headache</td>
<td>Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque</td>
</tr>
<tr>
<td>Estrogen-withdrawal headache</td>
<td>Painful trigeminal neuropathy attributed to space-occupying lesion</td>
</tr>
<tr>
<td><strong>HEADACHE ATTRIBUTED TO INFECTION</strong></td>
<td>Painful trigeminal neuropathy attributed to other disorder</td>
</tr>
<tr>
<td>Acute or chronic headache attributed to bacterial meningitis or meningoecephalitis</td>
<td>Glossopharyngeal neuralgia</td>
</tr>
<tr>
<td>Persistent headache attributed to past bacterial meningitis or meningoecephalitis</td>
<td>Classical nervus intermedius (facial nerve) neuralgia</td>
</tr>
<tr>
<td>Acute or chronic headache attributed to intracranial fungal or other parasitic infection</td>
<td>Nervus intermedius neuropathy attributed to herpes zoster</td>
</tr>
<tr>
<td>Headache attributed to brain abscess</td>
<td>Occipital neuralgia</td>
</tr>
<tr>
<td>Headache attributed to subdural empyema</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Headache attributed to systemic infection (acute or chronic)</td>
<td>Headache attributed to ischemic ocular motor nerve palsy</td>
</tr>
<tr>
<td><strong>HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS</strong></td>
<td>Tolosa-Hunt syndrome</td>
</tr>
<tr>
<td>Headache attributed to hypoxia and/or hypercapnia</td>
<td>Paratrigeminal oculosympathetic (Raeder) syndrome</td>
</tr>
<tr>
<td>High-altitude headache</td>
<td>Recurrent painful ophthalmoletic neuropathy</td>
</tr>
<tr>
<td>Headache attributed to airplane travel</td>
<td>Burning mouth syndrome (BMS)</td>
</tr>
<tr>
<td>Diving headache</td>
<td>Persistent idiopathic facial pain (PIFP)</td>
</tr>
<tr>
<td>Sleep apnea headache</td>
<td>Central neuropathic pain</td>
</tr>
<tr>
<td>Dialysis headache</td>
<td>Central neuropathic pain attributed to multiple sclerosis (MS)</td>
</tr>
<tr>
<td>Headache attributed to arterial hypertension</td>
<td>Central post-stroke pain (CPS)</td>
</tr>
<tr>
<td>Headache attributed to pheochromocytoma</td>
<td><strong>HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE</strong></td>
</tr>
<tr>
<td>Headache attributed to hypertensive crisis with or without hypertensive en cephalopathy</td>
<td>Headache attributed to disorder of cranial bone</td>
</tr>
<tr>
<td>Headache attributed to preeclampsia or eclampsia</td>
<td>Headache attributed to retropharyngeal tendinitis</td>
</tr>
<tr>
<td>Headache attributed to acute glaucoma</td>
<td>Headache attributed to craniocervical dystonia</td>
</tr>
<tr>
<td>Headache attributed to refractive error</td>
<td>Headache attributed to acute glaucoma</td>
</tr>
<tr>
<td>Headache attributed to heterophoria or heterotropia (latent or persistent squint)</td>
<td>Headache attributed to refractive error</td>
</tr>
<tr>
<td>Headache attributed to ocular inflammatory disorder</td>
<td>Headache attributed to disorder of the ears</td>
</tr>
<tr>
<td>Headache attributed to trachilis</td>
<td>Headache attributed to acute or chronic or recurring rhinosinusitis</td>
</tr>
<tr>
<td>Headache attributed to temporomandibular disorder (TMD)</td>
<td>Headache attributed to temporomandibular disorder (TMD)</td>
</tr>
<tr>
<td>Head or facial pain attributed to inflammation of the stylohyoid ligament</td>
<td>Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure</td>
</tr>
</tbody>
</table>

595.1 Migraine

Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O’Brien

Migraine is the most frequent type of recurrent headache that is brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children. Migraine is characterized by episodic attacks that may be moderate to severe in intensity, focal in location on the head, have a throbbing quality, and may be associated with nausea, vomiting, light sensitivity, and sound sensitivity. Compared to adults, pediatric migraine is shorter in duration and has a bilateral, often bifrontal, location. Migraine can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (i.e., hemiplegic, “Alice in Wonderland” syndrome) (Tables 595-2 to 595-6). In addition, a number of migraine variants have been described and, in children, include abdominal related symptoms without headache, and components of the painless periodic syndromes of childhood (see Table 595-1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

Epidemiology

Up to 75% of children report having a significant headache by the time they are 15 yr old. Recurrent headaches are less common, but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 yr, and up to 28% of older children.

Table 595-2 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Table 595-3 Migraine with Typical Aura

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded


Table 595-4 Migraine with Brainstem Aura

A. At least 2 attacks fulfilling criteria B to D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness
D. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded


Table 595-5 Vestibular Migraine with Vertigo

A. At least 5 episodes fulfilling criteria C and D
B. A current or past history of 1.1 Migraine without aura or 1.2 Migraine with aura
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
D. At least 50% of episodes are associated with at least 1 of the following 3 migraineous features:
   1. Headache with at least 2 of the following 4 characteristics:
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe intensity
      d. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder


Table 595-6 Chronic Migraine

A. Headache (tension-type-like and/or migraine-like) on 15 or more days per month for more than 3 mo and fulfilling criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C. On 8 or more days per month for more than 3 mo, fulfilling any of the following:
   1. Criteria C and D for 1.1 Migraine without aura
   2. Criteria B and C for 1.2 Migraine with aura
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
   4. Not better accounted for by another ICHD-3 diagnosis

adolescents. When the headaches become frequent, they convert into chronic daily headaches in up to 1% of children. When headaches are occurring more than 15 days a month the risk of conversion to a daily headache becomes more prominent. This explains the necessity to treat the headaches aggressively or prevent the headaches altogether, trying to block transformation to chronic daily headaches.

Migraine can impact a patient's life through school absences, limitation of home activities, and restriction of social activities. As headaches become more frequent, their negative impact increases in magnitude. This can lead to further complications including anxiety and school avoidance, requiring a more extensive treatment plan.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Criteria have been established to guide the clinical and scientific study of headaches; these are summarized in The International Classification of Headache Disorders, 3rd edition (ICHD-3 beta). Table 595-1 contrasts the different clinical types of migraine; Tables 595-2 to 595-6 list the specific criteria for migraine types.

Migraine Without Aura

Migraine without aura is the most common form of migraine in both children and adults. The ICHD-3 beta (see Table 595-2) requires this to be recurrent (at least 5 headaches that meet the criteria, but there is no time limit over which this must occur). The recurrent episodic nature helps differentiate this from a secondary headache, as well as separates migraine from tension-type headache, but may limit the diagnosis in children as they may just be beginning to have headaches.

The duration of the headache is defined as 4-72 hr for adults. It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce this duration to 2-72 hr or 1-72 hr with diary confirmation. Note that this duration is for the untreated or unsuccessfully treated headache. Furthermore, if the child falls asleep with the headache, the entire sleep period is considered part of the duration. These duration limits help differentiate migraine from both short-duration headaches, including the trigeminal autonomic cephalalgias, and prolonged headaches, like those caused by idiopathic intracranial hypertension (pseudotumor cerebri). Some prolonged headaches may still be migraine, but a migraine that persists beyond 72 hr is classified as a variant termed status migrainosus.

The quality of migraine pain is often, but not always, throbbing or pounding. This may be difficult to elicit in young children and draw-ings or demonstrations may help confirm the throbbing quality.

The location of the pain has classically been described as unilateral (hemicrania); in young children it is more commonly bilateral. A more approximate way to think of the location would therefore be focal, to differentiate it from the diffuse pain of tension-type headaches. Of particular concern is the exclusively occipital headache because although these can be migraines, they are more frequently secondary to another more proximate etiology such as posterior fossa abnormalities.

Migraine, when allowed to fully develop, often worsens in the face of and secondarily results in altered activity level. For example, worsening of the pain occurs classically in adults when going up or down stairs. This history is often not elicited in children. A change in the child's activity pattern can be easily observed as a reduction in play or physical activity. Older children may limit or restrict their sports activity or exercise during a headache attack.

Migraine may have a variety of associated symptoms. In younger children, nausea and vomiting may be the most obvious symptoms and often outweigh the headache itself. This often leads to the overlap with several of the gastrointestinal periodic diseases, including recurrent abdominal pain, recurrent vomiting, cyclic vomiting, and abdominal migraine. The common feature among all of these related conditions is an increased propensity among children with them for the later development of migraine. Oftentimes, early childhood recurrent vomiting may in fact be migraine, but the child is not asked about or is unable to describe headache pain. Once this becomes clear, the earlier diagnosis of a gastrointestinal disorder is no longer appropriate. When headache is present, vomiting raises the concern of a secondary headache, particularly related to increased intracranial pressure. One of the red flags for this is the daily or near daily early morning vomiting, or headaches waking the child up from sleep. When the headaches associated with vomiting episodes are sporadic and not worsening, it is more likely that the diagnosis is migraine. Vomiting and headache caused by increased intracranial pressure are frequently present on first awakening and remit with maintenance of upright posture. In contrast, if a migraine is present on first awakening (a relatively infrequent occurrence in children), getting up and going about normal, upright activities usually makes the headache and vomiting worse.

As the child matures, light and sound sensitivity (photophobia and phonophobia) may become more apparent. This is either by direct report of the patient, or the interpretation by the parents of the child's activity. These symptoms are likely a component of the hypersensitivity that develops during an acute migraine attack and may also include smell sensitivity (osmophobia) and touch sensitivity (cutaneous allodynia with central sensitization). Although only the photophobia and phonophobia are components of the ICHD-3 beta criteria, these other symptoms are helpful in confirming the diagnosis and may be helpful in understanding the underlying pathophysiology and determining the response to treatment. The final ICHD-3 beta requirement is the exclusion of causes of secondary headaches, and this should be an integral component of the headache history.

Migraine typically runs in families with reports up to 90% of children having a 1st- or 2nd-degree relative with recurrent headaches. Given the underdiagnosis and misdiagnosis in adults, this is often not recognized by the family and a headache family history is required. When a family history is not identified, this may be the result of either a lack of awareness of migraine within the family or an underlying secondary headache in the child. Any child whose family, upon close and both direct and indirect questioning, does not include individuals with migraine or related syndromes (e.g., motion sickness, cyclic vomiting, menstrual headache) should have an imaging procedure performed to look for anatomic etiologies for headache.

In addition to the classifying features, there may additional markers of a migraine disorder. These include such things as triggers (skipping meals, inadequate or irregular sleep, dehydration and weather changes are the most common), pattern recognition (associated with menstrual periods in adolescents or Monday-morning headaches resulting from changes in sleep patterns over the weekend and nonphysiologic early waking on Monday mornings for school), and premonitory symptoms (a feeling of irritability, tiredness, and food cravings prior to the start of the headache). Although these additional features may not be consistent, they do raise the index of suspicion for migraine and provide a potential mechanism of intervention. In the past, food triggers were considered widely common, but the majority have either been discredited with scientific study or represent such a small number of patients that they only need to be addressed when consistently triggering the headache.

Migraine with Aura

The aura associated with migraine is a neurologic warning that a migraine is going to occur. In the common forms this can be the start of a typical migraine or a headache without migraine, or it may even occur in isolation. For a typical aura, the aura needs to be visual, sensory, or dysphasic, lasting longer than 5 min and less than 60 min with the headache starting within 60 min (see Table 595-3). The importance of the aura lasting longer than 5 min is to differentiate the migraine aura from a seizure with a postictal headache, while the 60 min maximal duration is to separate migraine aura from the possibility of a more prolonged neurologic event such as a transient ischemic attack.

The most common type of visual aura in children and adolescents is photopsia (flashes of light or light bulbs going off everywhere). These photopsias are often multicolored and when gone, the child may report not being able to see where the flash occurred. Less likely in children are the typical adult auras including fortification spectra (brilliant white
zigzag lines resembling a starred pattern castle) or shimmering scotoma (sometimes described as a shining spot that grows or a sequined curtain closing). In adults, the auras typically involve only half the visual field, whereas in children they may be randomly dispersed. Blurred vision is often confused as an aura but is difficult to separate from photophobia or difficulty concentrating during the pain of the headache.

Sensory auras are less common. They typically occur unilaterally. Many children describe this sensation as insects are worms crawling from their hand, up their arm to their face with a numbness following this sensation. Once the numbness occurs, the child may have difficulty using the arm as they have lost sensory input, and a misdiagnosis of hemiplegic migraine may be made.

Dysphasic auras are the least-common type of typical aura and have been described as an inability or difficulty to respond verbally. The patient will be able to understand what is being asked, but cannot answer back. This may be the basis of what in the past has been referred to as confusional migraine and special attention needs to be paid to asking the child about this possibility and their degree of understanding during the initial phases of the attack. Most of the time, these episodes are described as a motor aphasia and they are often associated with sensory or motor symptoms.

Much less commonly, atypical forms of aura can occur, including hemiplegia (true weakness, not numbness, and may be familial), vertigo or lower cranial nerve symptoms (basilar-type, formerly thought to be caused by basilar artery dysfunction, now thought to be more brainstem based) (see Table 395-4), and distortion (“Alice in Wonderland” syndrome). Whenever these rarer forms of aura are present, further investigation is warranted. Not all motor auras can be classified as hemiplegic migraine spectrum and they should be differentiated from those very specific migrainous events, as the diagnosis of hemiplegic migraine has genetic, pathophysiologic, and therapeutic implications.

Hemiplegic migraine is one of the better known forms of rare auras. This transient unilateral weakness usually lasts only a few hours but may persist for days. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with mutations described in 3 separate genes: (1) CACNA1A, (2) ATP1A2, and (3) SCN1A. Some patients with familial hemiplegic migraine have other yet-to-be-identified genetic mutations. Multiple polymorphisms have been described for these genes. Hemiplegic migraines may be triggered by minor head trauma, exertion, or emotional stress. The motor weakness is usually associated with another aura symptom and may progress slowly over 20–30 min first with visual and then followed in sequence by sensory, motor, aphasic, and then basilar auras. Headache is present in more than 95% of patients and usually begins during the aura; headache may be unilateral or bilateral and may have no relationship to the motor weakness. Some patients may develop attacks of coma with encephalopathy, cerebrospinal fluid (CSF) pleocytosis, and cerebral edema. Long-term complications may include seizures, repetitive daily episodes of blindness, cerebellar signs with the development of cerebellar atrophy, and mental retardation.

Basilar-type migraine was formerly considered a disease of the basilar artery as many of the unique symptoms were attributed to dysfunction in this area of the brainstem. Some of the symptoms described include vertigo, tinnitus, diplopia, blurred vision, scotoma, ataxia, and an occipital headache. The pupils may be dilated, and ptosis may be evident.

Syndrome of transient headache and neurologic deficits with CSF lymphocytosis (HaNDL) describes transient headaches associated with neurologic deficits, and CSF showing pleocytosis. It is considered a self-limited migraine-like syndrome, and is rarely reported in the pediatric population.

Childhood periodic syndromes are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleep talking, and night terrors), unexplained recurrent fevers, and even seizures.

The gastrointestinal symptoms span the spectrum from the relatively mild (motion sickness on occasional long car rides) to severe episodes of uncontrollable vomiting that may lead to dehydration and the need for hospital admission to receive fluids. These latter episodes may occur on a predictable time schedule and hence have been called cyclic vomiting. During these attacks, the child may appear pale and frightened but does not lose consciousness. After a period of deep sleep, the child awakens and resumes normal play and eating habits as if the vomiting had not occurred. Many children with cyclic vomiting have a positive family history of migraine, and as they grow older have a higher than average likelihood of developing migraine. Cyclic vomiting may be responsive to migraine-specific therapies with careful attention to fluid replacement if the vomiting is excessive. Cyclic vomiting of migraine must be differentiated from gastrointestinal disorders including intestinal obstruction (malrotation, intermittent volvulus, duodenal web, duplication cysts, superior mesenteric artery compression, and internal hernias), peptic ulcer, gastritis, giardiasis, chronic pancreatitis, and Crohn disease. Abnormal gastrointestinal motility and pleviureteric junction obstruction can also cause cyclic vomiting. Metabolic causes include disorders of amino acid metabolism (heterozygote ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia, methylmalonic acidemia), fatty acid oxidation defects (medium-chain acyl-coenzyme A dehydrogenase deficiency), disorders of carbohydrate metabolism (hereditary fructose intolerance), acute intermittent porphyria, and structural central nervous system lesions (posterior fossa brain tumors, subdural hematomas or effusions). The diagnosis is a diagnosis of exclusion and children will need a full work up prior to be labeled of cyclic vomiting syndrome. Cyclic vomiting syndrome is more frequent in younger children and will gradually transform into a typical migraine attack by puberty.

The diagnosis of abdominal migraine can be confusing but can be thought of as a migraine without the headache. Like a migraine, it is an episodic disorder characterized by midabdominal pain with pain-free periods between attacks. At times this pain is associated with nausea and vomiting (thus crossing into the recurrent abdominal pain or cyclic vomiting spectrum). The pain is usually described as “dull” and may be moderate to severe. The pain may persist from 1–72 hr and, although usually midline, may be periumbilical or poorly localized by the child. To meet the criteria of abdominal migraine, the child must complain at the time of the abdominal pain of at least 2 of the following: anorexia, nausea, vomiting, or pallor. As with cyclic vomiting, a thorough history and physical examination with appropriate laboratory studies must be completed to rule out an underlying gastrointestinal disorder as a cause of the abdominal pain. Careful questioning about the presence of headache or head pain needs to be addressed directly with the child, as many times this is truly a migraine, but in the child’s mind (as well as the parents’ observation) the abdominal symptoms are paramount.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

A thorough history and physical examination including a neurologic examination with special focus on headache has been shown to be the most sensitive indicator of an underlying etiology. The history needs to include a thorough evaluation of the premonitory symptoms, any potential triggering events or timing of the headaches, associated neurologic symptoms, and a detailed characterization of the headache attacks, including frequency, severity, duration, associated symptoms, use of medication, and disability. The disability assessment should include the impact on school, home, and social activities and can easily be assessed with tools such as PedMIDAS. Family history of headaches and any other neurologic, psychiatric, and general health conditions is also important both for identification of migraine within the family as well as the identification of possible secondary headache disorders. The familial penetrance of migraine is so robust that the absence of a family history of migraine or its equivalent phenomena should trigger obtaining of an imaging procedure. When headaches are refractory, a history of potential comorbid conditions, which includes mood disorders and
illicit substance use, especially in teenagers, that may influence adherence and acceptability of the treatment plan, may also need to be addressed.

Neuroimaging is warranted when the neurologic examination is abnormal or unusual neurologic features occur during the migraine; when the child has headaches that awaken the child from sleep or that are present on first awakening and remit with upright posture; when the child has brief headaches that only occur with cough or bending over; when the headache is mostly in the occipital area; and when the child has migrainous headache with an absolutely negative family history of migraine or its equivalent (e.g., motion sickness, cyclic vomiting; Table 595-7). In this case, an MRI is the imaging of choice as it provides the highest sensitivity for detecting posterior fossa lesions and does not expose the child to radiation.

In the child with a headache that is instantaneously at its worst at onset, a CT scan looking for blood is the best initial test; and, if it is negative, a lumbar puncture should be done looking especially for xanthochromia of the CSF. There is no evidence that laboratory studies or an electroencephalogram is beneficial in a typical migraine without aura or migraine with aura.

**TREATMENT**

Table 595-8 outlines the drugs used to manage migraine headaches in children.

The American Academy of Neurology established useful practice guidelines for the management of migraine as follows:

1. Reduction of headache frequency, severity, duration, and disability
2. Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
3. Improvement in quality of life
4. Avoidance of acute headache medication escalation
5. Education and enabling of patients to manage their disease to enhance personal control of their migraine
6. Reduction of headache-related distress and psychologic symptoms

**Table 595-7**

### Indications for Neuroimaging in a Child with Headaches

<table>
<thead>
<tr>
<th>Abnormal neurologic examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal or focal neurologic signs or symptoms</td>
</tr>
<tr>
<td>Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)</td>
</tr>
<tr>
<td>Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase</td>
</tr>
<tr>
<td>Seizures or very brief auras (&lt;5 min)</td>
</tr>
<tr>
<td>Unusual headaches in children</td>
</tr>
<tr>
<td>Atypical auras including basilar-type, hemiplegic</td>
</tr>
<tr>
<td>Trigeminal autonomic cephalalgia including cluster headaches in child or adolescent</td>
</tr>
<tr>
<td>An acute secondary headache (i.e., headache with known underlying illness or insult)</td>
</tr>
<tr>
<td>Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache</td>
</tr>
<tr>
<td>Brief cough headache in a child or adolescent</td>
</tr>
<tr>
<td>Headache worst on first awakening or that awakens the child from sleep</td>
</tr>
<tr>
<td>Migrainous headache in the child with no family history of migraine or its equivalent</td>
</tr>
</tbody>
</table>

**Table 595-8**

### Drugs Used in the Management of Migraine Headaches in Children

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>MECHANISM</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACETAMINOPHEN</td>
<td>15 mg/kg/dose</td>
<td>Analgesic effects</td>
<td>Overdose, fatal hepatic necrosis</td>
<td>Effectiveness limited in migraine</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>7.5-10 mg/kg/dose</td>
<td>Antiinflammatory and analgesic</td>
<td>GI bleeding stomach upset, kidney injury</td>
<td>Avoid overuse (2-3 times per wk)</td>
</tr>
<tr>
<td><strong>TRIPTANS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan* (ages 12-17 yr)</td>
<td>12.5 mg</td>
<td>5-HT&lt;sub&gt;1b/1d&lt;/sub&gt; agonist</td>
<td>Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort</td>
<td>Avoid overuse (more than 4-6 times per mo)</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>40 mg</td>
<td>Same</td>
<td>Same</td>
<td>Avoid overuse (more than 4-6 times per mo)</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2.5 mg</td>
<td>Same</td>
<td>Same</td>
<td>May be effective for menstrual migraine prevention</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>2.5 mg</td>
<td>Same</td>
<td>Same</td>
<td>May be effective for menstrual migraine prevention</td>
</tr>
<tr>
<td>Rizatriptan* (ages 6-17 yr)</td>
<td>5 mg for child weighing &lt;40 kg, 10 mg</td>
<td>Same</td>
<td>Same</td>
<td>Available in tablets and melts</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Oral: 25 mg, 50 mg, 100 mg Nasal: 10 mg</td>
<td>Same</td>
<td>Same</td>
<td>Avoid overuse (more than 4-6 times per mo)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Oral: 2.5 mg, 5 mg Nasal: 5 mg</td>
<td>Same</td>
<td>Same</td>
<td>Available in tablets and melts</td>
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</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>MECHANISM</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>5 mg hs</td>
<td>Calcium channel blocking agent</td>
<td>Headache, lethargy, dizziness</td>
<td>May ↑ to 10 mg hs</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>20 mg/kg/24 hr (begin 5 mg/kg/24 hr)</td>
<td>↑ Brain GABA</td>
<td>Nausea, pancreatitis, fatal hepatotoxicity</td>
<td>↑ 5 mg/kg every 2 wk</td>
</tr>
<tr>
<td>Topiramate</td>
<td>100-200 mg divided bid</td>
<td>↑ Activity of GABA</td>
<td>Fatigue, nervousness</td>
<td>Increase slowly over 12-16 wk</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>20-60 mg/kg divided bid</td>
<td>Unknown</td>
<td>Irritability, fatigue</td>
<td>Increase every 2 wk starting at 20 mg/kg divided bid</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900-1800 mg divided bid</td>
<td>Unknown</td>
<td>Somnolence, fatigue aggression, weight gain</td>
<td>Begin 300 mg, ↑ 300 mg/wk</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>1 mg/kg/day</td>
<td>↑ CNS serotonin and norepinephrine</td>
<td>Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion</td>
<td>Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr</td>
<td>H1-receptor and serotonin agonist</td>
<td>Drowsiness, thick bronchial secretions</td>
<td>Preferred in children who cannot swallow pills; not well tolerated in adolescents</td>
</tr>
<tr>
<td><strong>Antihypertensive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>10-20 mg tid</td>
<td>Nonselective β-adrenergic blocking agent</td>
<td>Dizziness, lethargy</td>
<td>Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>1-3 mg/kg/day</td>
<td>Increases fatty acid oxidation in mitochondria</td>
<td>No adverse effects reported</td>
<td>Fat soluble; ensure brand contains small amount of vitamin E to help absorption</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>50-400 mg daily</td>
<td>Cofactor in energy metabolism</td>
<td>Bright yellow urine, polyuria and diarrhea</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>9 mg/kg divided tid</td>
<td>Cofactor in energy metabolism</td>
<td>Diarrhea or soft stool</td>
<td></td>
</tr>
<tr>
<td>Butterbur</td>
<td>50-150 mg daily</td>
<td>May act similar to a calcium channel blocker</td>
<td>Burping</td>
<td></td>
</tr>
<tr>
<td>Onabotulinumtoxin A</td>
<td>100 units (age 11-17 yr)</td>
<td>Inhibits acetylcholine release from nerve endings</td>
<td>Ptosis, blurred vision, hematoma at injection site</td>
<td>Used off label in children</td>
</tr>
<tr>
<td><strong>SEVERE INTRACTABLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>0.15 mg/kg/IV; max dose 10 mg</td>
<td>Dopamine antagonist</td>
<td>Agitation, drowsiness, muscle stiffness, akinesia and akathisia</td>
<td>May have increased effectiveness when combined with ketorolac and fluid hydration</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>0.2 mg/kg IV; 10 mg max dose</td>
<td>Dopamine antagonist</td>
<td>Drowsiness, urticaria, agitation, akinesia and akathisia</td>
<td>Caution in asthma patients</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.5 mg/kg IV; 15 mg max dose</td>
<td>Antiinflammatory and analgesic ↑ Brain GABA</td>
<td>GI upset, bleeding</td>
<td></td>
</tr>
<tr>
<td>Valproate sodium injection</td>
<td>15 mg/kg IV; 1,000 mg max dose</td>
<td>Dopamine antagonist</td>
<td>Nausea, vomiting, somnolence, thrombocytopenia</td>
<td>Would avoid in hepatic disease</td>
</tr>
<tr>
<td>Dihydroergotamine IV</td>
<td>0.5 mg/dose every 8 hr (&lt;40 kg)</td>
<td>Antiinflammatory and analgesic ↑ Brain GABA</td>
<td>Nausea, vomiting, vascular constriction, phlebitis</td>
<td>Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase).</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>0.5-1.0 mg/dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FDA approved in the pediatric population.
† Available in Europe.
↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.
To accomplish these goals, 3 components need to be incorporated into the treatment plan:

1. An acute treatment strategy should be developed for stopping a headache attack on a consistent basis with return to function as soon as possible with the goal being 2 hr maximum.
2. A preventive treatment strategy should be considered when the headaches are frequent (1 or more per week) and disabling.
3. Biobehavioral therapy should be started, including a discussion of adherence, elimination of barriers to treatment, and healthy habit management.

Acute Treatment
Management of an acute attack is to provide headache freedom as quickly as possible with return to normal function. This mainly includes 2 groups of medicines: nonsteroidal antiinflammatory drugs (NSAIDs) and triptans. Most migraine headaches in children will respond to appropriate doses of NSAIDs when administered at the onset of the headache attack. Ibuprofen has been well documented to be effective at a dose of 7.5-10.0 mg/kg and is often preferred; however, acetaminophen (15 mg/kg) can be effective in those with a contraindication to NSAIDs. Special concern for the use of ibuprofen or other NSAIDs includes ensuring that the children can recognize and respond to onset of the headache. This means discussing with the child the importance of telling the teacher when the headache starts at school and ensuring that proper dosing guidelines and permission have been provided to the school. In addition, overuse needs to be avoided, limiting the NSAID (or any combination of nonprescription analgesics) to not more than 2-3 times per week. The limitation of any analgesic to not more than 3 headaches a week is necessary to prevent the transformation of the migraines into medication overuse headaches. If a patient has maximized the weekly allowance of analgesics, the patient's next step is to only use hydrating fluids for the rest of the week as an abortive approach. If ibuprofen is not effective, naproxen sodium also may be tried in similar doses. Aspirin is also a reasonable option but is usually reserved for older children (older than age 15 yr). Use of other NSAIDs have yet to be studied in pediatric migraine. The goal of the primary acute medication should be headache relief within 1 hr with return to function in 10 of 10 headaches.

When a migraine is especially severe, NSAIDs alone may not be sufficient. In this case, a triptan may be considered. Multiple studies have demonstrated their effectiveness and tolerability. There are currently 2 triptans that are approved by the FDA for the treatment of episodic migraine in the pediatric population. Almotriptan is approved for the treatment of acute migraine in adolescents (ages 12-17 yr). Rizatriptan is approved for the treatment of migraine in children as young as age 6 yr. The combination of naproxen sodium and sumatriptan has been studied and may be effective in children. Controlled clinical trials demonstrate that intranasal sumatriptan is safe and effective in children older than age 8 yr with moderate to severe migraine. At present, pediatric studies showing the effectiveness of oral sumatriptan are lacking and there is insufficient evidence to support the use of subcutaneous sumatriptan in children. For most adolescents, dosing is the same as for adults; a reduction in dose is made for children weighing less than 40 kg. The triptans vary by rapidity of onset and biologic half-life. This is related to both their variable lipophilicity and dose. Clinically, 60-70% of patients respond to the first triptan tried, with 60-70% of the patients who did not respond to the first triptan responding to the next triptan. Therefore, in the patient who does not respond to the first triptan in the desired way (rapid reproducible response without relapse or side effects), it is worthwhile to try a different triptan. The most common side effects of the triptans are caused by their mechanism of action—tightness in the jaw, chest, and fingers as a result of vascular constriction and a subsequent feeling of grogginess and fatigue from the central serotonin effect. The vascular constriction symptoms can be alleviated through adequate fluid hydration during an attack.

The most effective way to administer abortive treatment is to use NSAIDs first in mild to severe cases, restricting their use to fewer than 2-3 attacks per week, and adding the triptan for moderate to severe, or attacks that have failed NSAID use, restricting to not more than 4-6 attacks per month. For an acute attack, the NSAIDs can be repeated once in 3-4 hr if needed for that specific attack, and the triptans can be repeated once in 2 hr if needed. It is important to consider the various formulations available and a discussion of these options should be made with pediatric patients and their parents, especially if a child is unable to swallow pills or take an oral dose because of nausea.

As vascular dilation is a common feature of migraine that may be responsible for some of the facial flushing followed by paleness and the lightheaded feeling accompanying the attacks, fluid hydration should be integrated into the acute treatment plan. For oral hydration this can include the sports drinks that combine electrolytes and sugar to provide the intravascular rehydration.

Antiemetics were used for acute treatment of the nausea and vomiting. Further study has identified that their unique mechanism of effectiveness in headache treatment is related to their antagonism of dopaminergic neurotransmission. Therefore, the antiemetics with the most robust dopamine antagonism (i.e., prochlorperazine and metoclopramide) have the best efficacy. These can be very effective for status migrainous or a migraine that is unresponsive to the NSAIDs and triptans. They require intravenous administration, as other forms of administration of these drugs are less effective than the NSAIDs or triptans. When combined with ketorolac and intravenous fluids in the emergency department or an acute infusion center, intravenous antiemetics can be very effective. When they are not effective, further inpatient treatment may be required using dilydroergotamine (DHE) which will mean an admission to an inpatient unit for more aggressive therapy of an intractable attack.

Emergency Department Treatments for Intractable Headaches
When an acute migraine attack does not respond to an outpatient regimen and is disabling, other therapeutic approaches are available and may be necessary to prevent further increases in the frequency of headaches. These migraines fall into the classification of status migrainous and need infusion therapy and admission to the emergency room department or to an inpatient unit.

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medications such as prochlorperazine and metoclopramide; NSAIDs such as ketorolac and DHE; antiepileptic drugs such as sodium valproate; and triptans.

Antidopaminergic Drugs: Prochlorperazine and Metoclopramide. The use of these medications is not limited to controlling the nausea and vomiting often present during a migraine headache. Their potential pharmacologic effect may be a result of their dopaminergic antagonism to dopamine property and the underlying pathologic process involving the dopaminergic system during a migraine attack. Prochlorperazine is very effective in aborting an attack in the emergency room when given intravenously with a bolus of IV fluid. Results show a 75% improvement with 50% headache freedom at 1 hr and 95% improvement with 60% headache freedom at 3 hr. Prochlorperazine may be more effective than metoclopramide. The average dose of metoclopramide use is 0.13-0.15 mg/kg with a maximum dose of 10 mg given intravenously over 15 min. The average dose of prochlorperazine is 0.15 mg/kg with a maximum dose of 10 mg. These medications are usually well tolerated, but extrapyramidal reactions are more frequent in children compared to the older population. An acute extrapyramidal reaction can be controlled in the emergency room with 25-50 mg of diphenhydramine given IV.

Nonsteroidal Antiinflammatory Drugs: Ketorolac. It is known that an aseptic inflammation occurs in the central nervous system as a result of the effect of multiple reactive peptides in patients with migraines. Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement. When combined to prochlorperazine, the response rate jumps to 93%.
Antiepileptic Drugs: Sodium Valproate. Antiepileptic drugs have been used as prophylactic treatment for migraine headache for years with adequate double-blinded, controlled studies on their efficacy in adults. The mechanism in which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15-20 mg/kg push (over 10 min). This intravenous load is followed by an oral dose (15-20 mg/day) in the 4 hr after the injection. Patients may benefit from a short-term preventive treatment with an extended release form after discharge from the emergency room. Sodium valproate is usually well tolerated. Patients should be receiving a fluid load during the procedure to prevent a possible hypo-osmolar episode.

Triptans. Subcutaneous sumatriptan (0.06 mg/kg) has an overall efficacy of 72% at 30 min and 78% at 2 hr, with a recurrence rate of 6%. Because children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population. DHE, if recommended for the recurrences, should not be given in the 24 hr after triptan use. Triptans are contraindicated in patients treated with monoamine oxidase inhibitors. Triptans may potentially produce a serotonin syndrome in patients taking a serotonin reuptake inhibitor. Both triptans and ergotamine are contraindicated in hemiplegic migraines.

Dihydroergotamine. DHE is an old migraine medication used as a vasoconstrictor to abort the vascular phase of migraine headache. The effectiveness is discussed in detail in the section "Inpatient Management of Intractable Migraine and Status Migrinosus" below. One dose of DHE can be effective for abortive treatment in the emergency department. Emergency room treatment of migraine shows a recurrence rate of 29% at 48-72 hr, with 6% who need more aggressive therapy in an inpatient unit.

Inpatient Management of Intractable Migraine and Status Migrinosus

Six percent to 7% of patients fail acute treatment in the emergency department. These patients are usually admitted for a 3-5 day stay and receive extensive parenteral treatment. A child should be admitted to the hospital for a primary headache when the child is in status migrainous, has an exacerbation of a chronic severe headache, or is in an analgesic rebound headache. The goal of inpatient treatment is to control a disabling headache that has been unresponsive to other abortive therapy and is disabling to the child. Treatment protocols include the use of DHE, antimetics, sodium valproate and other drugs.

Dihydroergotamine. Ergots are one of the oldest treatments for migraine headache. DHE is a parenteral form used for acute exacerbations. Its effect is because of the 5HT1A-1B-1D-1F receptor agonist affinity and central vasoconstriction. DHE has a greater α-adrenergic antagonist activity and is less vasoconstrictive peripherally. Before initiation of an IV ergot protocol, a full history and neurologic examination should be obtained. Girls of childbearing age should be evaluated on pregnancy before administering ergots.

The DHE protocol consists of the following: Patients are premedicated with 0.13-0.15 mg/kg of prochlorperazine 30 min prior to the DHE dose (maximum of 3 prochlorperazine doses to prevent extrapyramidal syndrome, then other types of antiemetics should be used, such as ondansetron). A dose of 0.5-1.0 mg of DHE is used (depending on age and tolerability) every 8 hr until headache freedom. When headache ceases, an extra dose is given in an attempt to prevent recurrence after discharge. The response to this protocol is a 97% improvement and 77% headache freedom. Response starts being noticeable by the fifth dose and can reach its maximum effects after the 10th dose. Side effects of DHE include nausea, vomiting, abdominal discomfort, flushed face, increased blood pressure. The maximum dose used in this protocol is 15 mg total of DHE. During the hospital admission the patient is usually started on migraine prophylaxis depending on the patient's history and comorbid problems.

Sodium Valproate. Sodium valproate is used when DHE is contraindicated or has been ineffective. One adult study recommends the use of valproate sodium as follows: Bolus with 15 mg/kg (maximum of 1,000 mg), followed by 5 mg/kg every 8 hr until headache freedom or up to a maximum of 10 doses. Always give an extra dose after headache ceases. This protocol was studied in adults with chronic daily headaches and showed an 80% improvement. It is well tolerated and is useful in children when DHE is ineffective, contraindicated, or not tolerated.

Preventive Therapy

When the headaches are frequent (more than 1 headache/wk) or there are more than 1 disabling headache a month (missing school, home, or social activities, or a PEDMIDAS score higher than 20), preventive or prophylactic therapy is warranted. The goal of this therapy should be to reduce frequency (1-2 headaches or fewer per month) and disability (PEDMIDAS score <10). Prophylactic agents should be given for at least 4-6 mo at an adequate dose and then weaned over several weeks. Evidence in adult studies has begun to demonstrate that persistent frequent headaches foreshadow an increased risk of progression with decreased responsiveness and increased risk of refractoriness in the future. It is unclear whether this also occurs in children and/or adolescents and whether early treatment of headache in childhood prevents development of refractory headache in adulthood.

Multiple preventive medications have been utilized for migraine prophylaxis in children. When analyzed as part of a practice parameter, only 1 medication, flunarizine (a calcium channel blocking agent), demonstrated a level of effectiveness viewed as substantial; it is not available in the United States. Flunarizine is typically dosed at 5 mg orally daily and increased after 1 mo to 10 mg orally daily, with a month off of the drug every 4-6 mo.

The most commonly used preventive therapy for headache and migraine is amitriptyline. Typically, a dose of 1 mg/kg daily at dinner or in the evening is effective. However, this dose needs to be reached slowly (i.e., over weeks: with an increase every 2 wk until goal is reached) to minimize side effects and improve tolerability. The most common side effects are sleepiness and those related to amitriptyline's anticholinergic activity. Weight gain has been observed in adults using amitriptyline but is a less frequent occurrence in children. Amitriptyline does have the potential to exacerbate prolonged QT syndrome, so it should be avoided in patients with this diagnosis and looked for in patients on the drug who complain of rapid or irregular heart rate.

Antiepileptic medications are also used for migraine prophylaxis, with topiramate, valproic acid, and levetiracetam having been demonstrated to be effective in adults. There are limited studies in children for migraine prevention, but all of these medications have been assessed for safety and tolerability in children with epilepsy.

Topiramate has become widely used for migraine prophylaxis in adults. Topiramate was also demonstrated to be effective in an adolescent study. This study demonstrated that a 25 mg dose twice a day was equivalent to placebo, whereas a 50 mg dose twice a day was superior. Thus it appears that the adult dosing schedule is also effective in adolescents with an effective dosage range or 25 mg twice a day to 100 mg twice a day. This dose needs to be reached slowly to minimize the cognitive slowing associated with topiramate use. Additional side effects include weight loss, paresthesias, kidney stones, lowered bicarbonate levels, decreased sweating, and rarely glaucoma and changes in serum transaminases. In addition, in adolescent girls taking birth control pills, the lowering of the effectiveness of the birth control by topiramate needs to be discussed.

Valproic acid has long been used for epilepsy in children and has been demonstrated to be effective in migraine prophylaxis in adults. The effective dose in children appears to be 10 mg/kg orally twice a day. Side effects of weight gain, ovarian cysts, and changes in serum transaminases and platelet counts need to be monitored. Other anti-epileptics, including lamotrigine, levetiracetam, zonisamide, gabapentin, and pregabalin, are also used for migraine prevention.

β-Blockers have long been used for migraine prevention. The studies on β-blockers have a mixed response pattern with variability both between β-blockers and between patients with a given β-blocker. Propranolol is the best studied for pediatric migraine prevention with unequivocally positive results. The contraindication for use of
propranolol in children with asthma or allergic disorders or diabetes and the increased incidence of depression in adolescents using propranolol limit its use somewhat. It may be very effective for a mixed subtype of migraine (basilar-type migraine with postural orthostatic tachycardia syndrome). This syndrome has been reported to be responsive to propranolol. α-Blockers and calcium channel blockers, aside from flunarizine, also have been used in pediatric migraine; their effectiveness, however, remains unclear.

In very young children, cyproheptadine may be effective in prevention of migraine or the related variants. Young children tend to tolerate the increased appetite induced by the cyproheptadine and tend not to be subject to the lethargy seen in older children and adults; the weight gain is limiting once children start to enter puberty. Typical dosing is 0.1-0.2 mg/kg orally twice a day.

Nutraceuticals have become increasingly popular over the past few years, especially among families who prefer a more “natural” approach to headache treatment. Despite studies showing success of these therapies in adults, few studies have shown effectiveness in pediatric headaches. Riboflavin (vitamin B₂), at doses ranging from 25-400 mg, is the most widely studied with good results. Side effects are minimal and include bright yellow urine, diarrhea, and polyuria. Coenzyme Q10 supplementation may be effective in reducing migraine frequency at doses of 1-2 mg/kg/day. Butterbur is also effective in reducing headaches with minimal side effects, including burping. Use in children has been limited to avoid the potential toxicity of butterbur containing pyrrolizidine alkaloids, which are naturally contained and are a known carcinogen and toxic to the liver.

OnabotulinumtoxinA is the first medication FDA-approved for chronic migraine in adults. There are studies in children indicating its effectiveness; use in children is considered off-label. The limited available studies revealed the following: Average dose used was 188.5 units ± 32 units with a minimum dose of 75 units and maximum of 200 units. The average age of patients receiving the treatment was 16.8 ± 2.0 yr (minimum: 11; maximum: 21 yr old). OnabotulinumtoxinA injections improved disability scores (PedMIDAS) and headache frequency in pediatric chronic daily headache patients and chronic migraine in this age group. OnabotulinumtoxinA not only had a positive effect on the disability scoring for these young patients with headache, but was also able to transform the headaches from chronic daily to intermittent headache in more than 50% of the patients.

**Biobehavioral Therapy**

Biobehavioral evaluation and therapy is essential for effective migraine management. This includes identification of behavioral barriers to treatment, like a child’s shyness or limitation in notifying a teacher of the start of a migraine or a teacher’s unwillingness to accept the need for treatment. Additional barriers include a lack of recognition of the significance of their headache problem and reverting to “bad habits” once the headaches have responded to treatment. Adherence is equally important for acute and preventative treatment. The need to have a sustained response for long enough to prevent relapse (i.e., to stay on preventive medication) is often difficult when the child starts to feel better. Establishing a defined treatment goal (1-2 or fewer headaches per month for 4-6 mo) helps with acceptance.

As many of the potential triggers for frequent migraines (skipping meals, dehydration, decreased or altered sleep) are related to a child’s daily routine, a discussion of healthy habits is a component of biobehavioral therapy. This should include adequate fluid intake without caffeine, regular exercise, not skipping meals and making healthy food choices, and adequate (8-9 hr) sleep on a regular basis. Sleep is often difficult in adolescents, as middle and high schools often have very early start times, and the adolescent’s sleep architecture features a shift to later sleep onset and wakening. This has been one of the explanations for worsening headaches during the school year in general and at the beginning of the school year and week.

Biofeedback-assisted relaxation and cognitive behavioral therapy (usually in combination with amitriptyline) are effective for both acute and preventative therapy and may be incorporated into this multiple treatment strategy. This provides the child with a degree of self-control over the headaches and may further help the child cope with frequent headaches.

**Bibliography is available at Expert Consult.**

### 595.2 Secondary Headaches

**Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O’Brien**

Headaches can be a common symptom of other underlying illnesses. In recognition of this, the ICHD-3 beta has classified the potential secondary headaches (see Table 595-1). The key to the diagnosis of a secondary headache is to recognize the underlying cause and demonstrate a direct cause and effect. Until this has been demonstrated the diagnosis is speculative. This is especially true when the suspected etiology is common.

Common causes or suspected causes of secondary headaches in children include the sequelae of head trauma and sinusitis. **Posttraumatic headaches** sometimes occur in children who have not had a prior history of headaches and are temporally related to the initiating head injury. Frequently, though, these children have a family history of migraine or its equivalent. The head injury may be minor or major and the subsequent headache may be acute (resolves within 3 mo, most typically within 10 days) or chronic (longer than 15 days per month for more than 3 mo). Bed rest appears to be the most effective treatment for acute posttraumatic headache; magnesium supplementation and migraine prophylaxis may also be effective. When a child has a history of episodic headaches, the head trauma or the overuse of daily medications may lead to status migrainosus or chronic migraine and the diagnosis may be difficult to sort out.

**Sinus headache** is the most overdiagnosed form of recurrent headaches. Although no studies have evaluated the frequency of misdiagnosis of an underlying migraine as a sinus headache in children, in adults, it has been found that up to 90% of adults diagnosed as having a sinus headache by either themselves or their physician appear to have migraine. When headaches are recurrent and respond within hours to analgesics, migraine should be considered first. In the absence of purulent nasal discharge, fever, or chronic cough, the diagnosis of sinus headache should not be made.

**Medication overuse headaches** frequently complicate primary and secondary headaches. A medication overuse headache is defined as a headache present for more than 15 days/mo for longer than 3 mo and intake of a simple analgesic on more than 15 days/mo and/or prescription medications including triptans or combination medications on more than 10 days/mo. Some of the signs that should raise suspicion of medication overuse are the increasing use of analgesics (nonprescription or prescription) with either decreased effectiveness or frequently wearing off (i.e., analgesic rebound). This can be worsened by using ineffective medications and underdosing or misdiagnosing the headache. Patients should be cautioned against the frequent use of antimigraine medications, including combination analgesics or triptans.

Serious causes of secondary headaches are likely to be related to increased intracranial pressure. This can be caused by a mass (tumor, vascular malformation, cystic structure) or an intrinsic increase in pressure (idiopathic intracranial hypertension also known as pseudotumor cerebri). In the former case, the headache is caused by the mass effect and local pressure on the dura; in the latter case, the headache is caused by diffuse pressure on the dura. The etiology of idiopathic intracranial hypertension may be the intake of excessive amounts of fat-soluble compounds (e.g., vitamin A, retinoic acid, and minocy clocline), hormonal changes (increased incidence in females) or blockage of venous drainage (as with inflammation of the transverse venous sinus from mastoiditis). When increased pressure is suspected, either by historical suspicion or the presence of papilledema, an MRI with magnetic resonance angiography and magnetic resonance venography should be performed, followed by a lumbar puncture if no mass or
Evaluation of patients with suspected TTHs requires a detailed headache history and complete general and neurologic examination. This is to establish the diagnosis and ensure exclusion of secondary etiologies. When secondary headaches are suspected, further, directed evaluation is indicated.

Treatment of TTHs can require acute therapy to stop attacks, preventive therapy when frequent or chronic, and behavioral therapy. It is often suspected that there may be underlying psychologic stressors (hence the misnomer as a "stress" headache), but this is often difficult to identify in children, and although it may be suspected by the parents, it cannot be confirmed in the child. Studies of and conclusive evidence to guide the treatment of TTH in children are lacking, but the same general principles and medications used in migraine can be applied to children with TTHs (see Chapter 595.1). Oftentimes, simple analgesics (ibuprofen or acetaminophen) can be effective for acute treatment. Flupirtine is a nonopioid analgesic that has been approved in Europe for the treatment of TTH in children as young as age 6 yr, but is not available in the United States. Amitriptyline has the most evidence of effective prevention of TTH; biobehavioral intervention, including biofeedback-assisted relaxation training and coping skills, can be useful as well.

Bibliography is available at Expert Consult.

595.3 Tension-Type Headaches
Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O’Brien

Tension-type headaches (TTHs) may be very common in children and adolescents with prevalence in some studies shown as high as 48%, with those having a combination of migraine and TTH around 20%. Because of their mild to moderate nature, relative lack of associated symptoms and lower degree of associated disability they are often ignored or have a minimal impact. The ICHD-3 beta subclassifies TTHs as infrequent (<12 times/yr) (Table 595-9), frequent (1-15 times/mo), and chronic (>15 headaches/mo). They can further be separated into headaches with or without pericranial muscle tenderness. The classification of TTH can be likened to the opposite of migraine. Whereas migraines are typically moderate to severe, are focal in location, are worsened by physical activity or limit physical activity, and have a throbbing quality, TTH are mild to moderate in severity, are diffuse in location, are not affected by activity (although the patient may not feel like being active), and are nonthrobbing (often described as a constant pressure). TTH is much less frequently associated with nausea, photophobia, or phonophobia and is never associated with more than 1 of these at a time or with vomiting. TTH must be recurrent, but at least 10 headaches are required and the duration can be 30 min to 7 days. Secondary headaches with other underlying etiologies must be ruled out.

Table 595-9 Infrequent Episodic Tension-Type Headache

| A. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B to D |
| B. Lasting from 30 min to 7 days |
| C. At least 2 of the following 4 characteristics: |
| 1. Bilateral location |
| 2. Pressing or tightening (nonpulsating) quality |
| 3. Mild or moderate intensity |
| 4. Not aggravated by routine physical activity such as walking or climbing stairs |
| D. Both of the following: |
| 1. No nausea or vomiting |
| 2. No more than 1 of photophobia or phonophobia |
| E. Not better accounted for by another ICHD-3 beta diagnosis |

Chapter 595  Headaches  2874.e1

Bibliography

**Bibliography**


The neurocutaneous syndromes include a heterogeneous group of disorders characterized by abnormalities of both the integument and central nervous system. Many of the disorders are familial and believed to arise from a defect in differentiation of the primitive ectoderm. Disorders classified as neurocutaneous syndromes include neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, von Hippel-Lindau disease, PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of aorta, cardiac defects, eye abnormalities) syndrome, ataxia telangiectasia, linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti.

596.1 Neurofibromatosis

Mustafa Sahin

Neurofibromatoses are autosomal dominant disorders that cause tumors to grow on nerves and result in other abnormalities such as skin changes and bone deformities. It was believed that there were 2 types of neurofibromatosis (type 1 and type 2), but it is recognized that they are clinically and genetically distinct diseases and should be considered separate entities: neurofibromatosis type 1 (NF-1) and neurofibromatosis type 2 (NF-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

NF-1 is the most prevalent type, with an incidence of 1 in 3,000 live births, and is caused by dominant loss-of-function mutations in the NF-1 gene. The disease is clinically diagnosed when any 2 of the following 7 features are present: (1) six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in greatest diameter in postpubertal individuals (Fig. 596-1). Café-au-lait spots are the hallmark of neurofibromatosis.
and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the 1st few yr of life. The spots are scattered over the body surface, with predilection for the trunk and extremities but sparing the face. (2) Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter. Skinfold freckling usually appears between 3 and 5 yr of age. The frequency of axillary and inguinal freckling is reported to be >80% by 6 yr of age. Café-au-lait macules are not specific for NF-1; they may be seen in Noonan syndrome, constitutional mismatch repair deficiency syndrome, Legius syndrome, Peutz-Jeghers syndrome, Carney complex, and those diseases listed in Table 596-1. (3) Two or more iris Lisch nodules. Lisch nodules are hamartomas located within the iris and are best identified by a slit-lamp examination (Fig. 596-2). They are present in more than 74% of patients with NF-1 but are not a characteristic of NF-2. The prevalence of Lisch nodules increases with age, from only 5% of children younger than 3 yr of age, to 42% among children 3-4 yr of age, and virtually 100% of adults older than 21 yr of age. (4) Two or more neurofibromas or 1 plexiform neurofibroma. Neurofibromas typically involve the skin, but they may be situated along peripheral nerves and blood vessels and within viscera including the gastrointestinal tract. Plexiform neurofibromas are usually evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of the face. The skin overlying a plexiform neurofibroma may be hyperpigmented to a greater degree than a café-au-lait macule. Plexiform
neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. (5) A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos) or cortical thinning of long bones with or without pseudoarthrosis (e.g., tibia). (6) Optic gliomas are present in approximately 15% of patients with NF-1 and represent mostly low-grade astrocytomas. They are the main central nervous system tumor with a marked increased frequency in NF-1. Because of their growth, it is recommended that all children age 10 yr or younger with NF-1 undergo annual ophthalmologic examinations. When they progress, visual symptoms occur because the tumors enlarge and put pressure on the optic nerves and chiasm resulting in impaired visual acuity and visual fields. Extension into the hypothalamus can lead to endocrine deficiencies or failure to thrive. The MRI findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm (Fig. 596-3). (7) A 1st-degree relative with NF-1 whose diagnosis was based on the aforementioned criteria.

Children with NF-1 are susceptible to neurologic complications. MRI studies of selected children have shown abnormal hyperintense T2-weighted signals in the optic tracts, brainstem, globus pallidus, thalamus, internal capsule, and cerebellum (Fig. 596-4). These signals, “unidentified bright objects,” tend to disappear with age; most have disappeared by 30 yr of age. It is unclear what the unidentified bright objects represent pathologically, and there is disagreement as to the relationship between the presence and number of unidentified bright objects and the occurrence of learning disabilities, attention-deficit disorders, behavioral and psychosocial problems, and abnormalities of speech among affected children. Therefore, imaging studies such as brain MRIs should be reserved for patients with clinical symptoms only.

One of the most common complications is learning disability affecting approximately 30% of children with NF-1. Seizures are observed in approximately 8% of NF-1 patients. The cerebral vessels may develop aneurysms or stenosis resulting in moyamoya syndrome (see Chapter 601). Neurologic sequelae of these vascular abnormalities include transient cerebrovascular ischemic attacks, hemiparesis, and cognitive defects. Precocious puberty may become evident in the presence or absence of lesions of the optic pathway tumors. Malignant neoplasms are also a significant problem in patients with NF-1, affecting approximately 3% of patients. A neurofibroma occasionally differentiates into a malignant peripheral nerve sheath tumor. The incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. Scoliosis is a common complication found in approximately 10% of the patients. Patients with NF-1 are at risk for hypertension, which may result from renal vascular stenosis or a pheochromocytoma.

**MANAGEMENT**

Because of the diverse and unpredictable complications associated with NF-1, close multidisciplinary follow-up is necessary. Patients with NF-1 should have regular clinical assessments at least yearly, focusing the history and examination on the potential problems for which they are at increased risk. These assessments include yearly ophthalmologic examination, neurologic assessment, blood pressure monitoring, and scoliosis evaluation. Neuropsychologic and educational testing should be considered as needed. The National Institutes of Health (NIH) Consensus Development Conference has advised against routine imaging studies of the brain and optic tracts because treatment in these


**Table 596-2** Frequency of Lesions Associated with Neurofibromatosis Type 2

<table>
<thead>
<tr>
<th>FREQUENCY OF ASSOCIATION WITH NF-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUROLOGIC LESIONS</td>
</tr>
<tr>
<td>Bilateral vestibular schwannomas</td>
</tr>
<tr>
<td>Other cranial nerve schwannomas</td>
</tr>
<tr>
<td>Intracranial meningiomas</td>
</tr>
<tr>
<td>Spinal tumors</td>
</tr>
<tr>
<td>Extramedullary</td>
</tr>
<tr>
<td>Intramedullary</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>OPHTHALMOLOGIC LESIONS</td>
</tr>
<tr>
<td>Cataracts</td>
</tr>
<tr>
<td>Epiretinal membranes</td>
</tr>
<tr>
<td>Retinal hamartomas</td>
</tr>
<tr>
<td>CUTANEOUS LESIONS</td>
</tr>
<tr>
<td>Skin tumors</td>
</tr>
<tr>
<td>Skin plaques</td>
</tr>
<tr>
<td>Subcutaneous tumors</td>
</tr>
<tr>
<td>Intradermal tumors</td>
</tr>
</tbody>
</table>


asymptomatic NF-1 children is rarely required. However, all symptomatic cases (i.e., those with visual disturbance, proptosis, increased intracranial pressure) must be studied without delay.

**GENETIC COUNSELING**

Although NF-1 is an autosomal dominant disorder, more than half the cases are sporadic, representing de novo mutations. The NF-1 gene on chromosome region 17q11.2 encodes for a protein also known as neurofibromin. Neurofibromin acts as an inhibitor of the oncogene Ras. The diagnosis of NF-1 is based on the clinical features. However, molecular testing for the NF-1 gene mutations is available and can be useful in a number of cases. Some scenarios in which genetic testing is helpful include for patients who meet only 1 of the criteria for clinical diagnosis, those with unusually severe disease, and those seeking prenatal/preimplantation diagnosis.

NF-2 is a rarer condition, with an incidence of 1 in 25,000 births, and may be diagnosed when 1 of the following 4 features is present: (1) bilateral vestibular schwannomas; (2) a parent, sibling, or child with NF-2 and either unilateral vestibular schwannoma or any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; (3) unilateral vestibular schwannoma and any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; or (4) multiple meningiomas (2 or more) and unilateral vestibular schwannoma or any 2 of the following: schwannoma, glioma, neurofibroma, cataract.

Symptoms of tinnitus, hearing loss, facial weakness, headache, or unsteadiness may appear during childhood, although signs of a cerebellopontine angle mass are more commonly present in the 2nd and 3rd decades of life. Although café-au-lait macules and skin neurofibromas are classic findings in NF-1, they are much less common in NF-2. Posterior subcapsular lens opacities are identified in approximately 50% of patients with NF-2. The NF-2 gene (which codes for a protein known as merlin or schwannomin) is located on chromosome 22q11.1. Table 596-2 notes the frequency of lesions in NF-2.

**Legius syndrome** (caused by SPRED1 mutations) resembles a mild form of NF-1. Patients with Legius syndrome present with multiple café-au-lait macules and macrocephaly, with and without skinfold freckling. However, other typical features of NF-1, such as Lisch nodules, neurofibromas, optic nerve gliomas, and malignant peripheral nerve sheath tumors, are not seen with SPRED1 mutations.

**596.2 Tuberous Sclerosis**

**Mustafa Sahin**

Tuberous sclerosis complex (TSC) is inherited in an autosomal dominant manner with variable expression and a prevalence of 1 in 6,000 newborns. Spontaneous genetic mutations occur in 65% of the cases. Molecular genetic studies have identified 2 loci for TSC: the TSC1 gene is located on chromosome 9q34, and the TSC2 gene is on chromosome 16p13. The TSC1 gene encodes a protein called hamartin, while the TSC2 gene encodes the protein tuberin. Within a cell, these 2 proteins bind to one another and work together. Consequently, a mutation in either the TSC1 gene or the TSC2 gene results in a similar disease in patients. The TSC1 and TSC2 genes are tumor-suppressor genes. The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas). Tuberin and hamartin are involved in a key pathway in the cell that regulates protein synthesis and cell size. One of the ways cells regulate their growth is by controlling the rate of protein synthesis. A protein called mTOR (mammalian target of rapamycin) was identified as one of the master regulators of cell growth. mTOR, in turn, is controlled by rhabdomyosarcoma, a small cytoplasmic guanosine triphosphatase. When rhabdomyosarcoma is activated, the protein synthesis machinery is turned on, most likely via mTOR, and the cell grows in size. Of interest in TSC, rhabdomyosarcoma is activated by the protein complex formed by hamartin and tuberin.

TSC is an extremely heterogeneous disease with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and a lack of seizures; this variation is often seen within the same family, thus with individuals carrying the same mutation. The disease affects many organ systems other than the skin and brain, including the heart, kidney, eyes, lungs, and bone (Fig. 596-5).

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

Definite TSC is diagnosed when at least 2 major or one major plus 2 minor features are present (Tables 596-3 and 596-4 list the major and minor features).

The hallmark of TSC is the involvement of the central nervous system. Retinal lesions consist of two types: hamartomas (elevated mulberry lesions or plaque-like lesions; Fig. 596-6) and white depigmented patches (similar to the hypopigmented skin lesions). The characteristic brain lesion is a cortical tuber (Fig. 596-7). Brain MRI is the best way of identifying cortical tubers, which can form before birth.

Subependymal nodules are lesions found along the wall of the lateral ventricles where they undergo calcification and project into the ventricular cavity, producing a “target sign” appearance. These lesions do not cause any problems; however, in 5-10% of cases, these benign lesions can grow into subependymal giant cell astrocytomas (SEGAs). These tumors can grow and block the circulation of cerebrospinal fluid around the brain and cause hydrocephalus, which requires immediate neurosurgical intervention. Thus, it is recommended that all asymptomatic TSC patients undergo brain MRI every 1-3 yr to monitor for new occurrence of SEGAs. Patients with large or growing SEGAs, or with SEGAs causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently and the patients and their families should be educated regarding the potential of new symptoms due to increased intracranial pressure. Surgical resection should be performed for acutely symptomatic SEGAs. For growing but otherwise asymptomatic SEGAs, either surgical resection or medical treatment with an mTOR inhibitor may be used. Presymptomatic treatment with everolimus is effective in slowing the growth or even reducing the size of SEGAs. Everolimus is also effective in treating refractory seizures and reducing the volume of renal angiomyolipomas and lymphangiomyomatosis as well as facial angiobromas.

The most common neurologic manifestations of TSC consist of epilepsy, cognitive impairment, and autism spectrum disorders. TSC may present during infancy with infantile spasms and a hypsarrhythmia electroencephalogram pattern. However, it is important to remember
Bibliography
that you can have infantile spasms without hypsarrhythmia in TSC patients. The seizures may be difficult to control and, at a later age, they may develop into myoclonic epilepsy (see Chapter 593). Vigabatrin is the first-line therapy for infantile spasms. ACTH can be used if treatment with vigabatrin fails. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies, and epilepsy surgery should be considered for medically refractory TSC patients.

**SKIN LESIONS**

More than 90% of patients show the typical hypomelanotic macules that have been likened to an ash leaf on the trunk and extremities. Visualization of the hypomelanotic macule is enhanced by the use of a Wood ultraviolet lamp (see Chapter 653). To count as a major feature, at least three hypomelanotic macules must be present (see Fig. 596-5). Facial angiofibromas develop between 4 and 6 yr of age; they appear as tiny red nodules over the nose and cheeks and are sometimes confused with acne (see Fig. 596-5). Later, they enlarge, coalesce, and assume a fleshy appearance. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located primarily in the lumbosacral region (see Fig. 596-5). During adolescence or later, small fibromas or nodules

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**Table 596-3** Major Features of TSC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical tuber</td>
<td>Subependymal nodule</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>Facial angiofibroma or forehead plaque</td>
</tr>
<tr>
<td>Ungual or periungual fibroma (non-traumatic)</td>
<td>Hypomelanotic macules (&gt;3)</td>
</tr>
<tr>
<td>Shagreen patch</td>
<td>Multiple retinal hamartomas</td>
</tr>
<tr>
<td>Cardiac rhabdomyoma</td>
<td>Renal angiomylipoma</td>
</tr>
<tr>
<td>Pulmonary lymphangioleiomyomatosis</td>
<td></td>
</tr>
</tbody>
</table>

**Table 596-4** Minor Features of TSC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral white matter migration lines</td>
<td>Multiple dental pits</td>
</tr>
<tr>
<td>Gingival fibromas</td>
<td>Bone cysts</td>
</tr>
<tr>
<td>Retinal achromatic patch</td>
<td>Confetti skin lesions</td>
</tr>
<tr>
<td>Nonrenal hamartomas</td>
<td>Multiple renal cysts</td>
</tr>
<tr>
<td>Hamartomatous rectal polyps</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 596-6** A mulberry lesion involving the superior part of the optic nerve in a patient with tuberous sclerosis. (From Yanoff M, Sassani JW: Ocular pathology, ed 7, Philadelphia, 2015, WB Saunders, Fig. 2-7.)
The current recommendation is to follow the angiomyolipoma by yearly imaging, and when the size of the lesion reaches more than 4 cm, to use transcatheter tumor embolization for treatment. Single or multiple renal cysts are also commonly present in TSC. Lymphangioleiomyomatosis is the classical pulmonary lesion in TSC and only affects women after the age of 20 yr.

Diagnosis of TSC relies on a high index of suspicion when assessing a child with infantile spasms. A careful evaluation for the typical skin and retinal lesions should be completed in all patients with a seizure disorder or autism spectrum disorder. Brain MRI confirms the diagnosis in most cases. Genetic testing for TSC1 and TSC2 mutations is available and may be considered when the individual patient does not meet all the clinical criteria. Prenatal testing may be offered when a known TSC mutation exists in that family.

**MANAGEMENT**

As for routine follow-up of individuals with TSC, the following are recommended in addition to physical examination: brain MRI every 1-3 yr, renal imaging (US, CT or MRI) every 1-3 yr and neurodevelopmental testing at the time of beginning 1st grade. Based on the complications of the disease, additional follow-up testing may be required for each individual. Symptoms and signs of increased intracranial pressure suggest obstruction of the foramen of Monro by a SEGA and warrant immediate investigation and surgical intervention.

*Bibliography is available at Expert Consult.*

**596.3 Sturge-Weber Syndrome**

*Mustafa Sahin*

Sturge-Weber syndrome (SWS) is a sporadic vascular disorder and consists of a constellation of symptoms and signs including a facial capillary malformation (port-wine stain), abnormal blood vessels of the brain (leptomeningeal angiom) and abnormal blood vessels of the eye leading to glaucoma. Patients present with seizures, hemiparesis, stroke-like episodes, headaches, and developmental delay. Approximately 1 in 50,000 live births are affected with SWS.

**OTHER ORGAN INVOLVEMENT**

Approximately 50% of children with TSC have cardiac rhabdomyomas, which may be detected in the fetus at by an echocardiogram. The rhabdomyomas may be numerous or located at the apex of the left ventricle, and although they can cause congestive heart failure and arrhythmias in a minority of patients, they tend to slowly resolve spontaneously. In 75-80% of patients older than 10 yr of age, the kidneys display angiomyolipomas that are usually benign tumors. Angiomyolipomas begin in childhood in many individuals with TSC, but they may not be problematic until young adulthood. By the third decade of life, they may cause lumbar pain and hematuria from slow bleeding, and rarely they may result in sudden retroperitoneal bleeding. Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy should be avoided. For asymptomatic, growing angiomyolipomas measuring larger than 3 cm in diameter, an mTOR inhibitor, everolimus, is FDA-approved for treatment. Selective embolization or kidney-sparing resection is alternative therapies for asymptomatic angiomyolipoma.
Bibliography


ETIOLOGY
The sporadic incidence and focal nature of SWS suggests the presence of somatic mutations. Whole-genome sequencing from affected and unaffected skin of 3 patients with SWS identified a single-nucleotide variant (c.548G→A, p.Arg183Gln) in the GNAQ gene. This mutation has been confirmed in samples of affected tissue from 88% of a larger cohort of SWS patients as well as 92% of the participants with apparently nonsyndromic port-wine stains. Brain tissue from SWS patients also demonstrated the same change in the GNAQ gene. These results strongly suggest that SWS occurs as a result of mosaic mutations in GNAQ.

The condition is thought to result from anomalous development of the embryonic vascular bed in the early stages of facial and cerebral development. There are hypotheses about aberrant sympathetic innervation, increased vascular growth factors and defects in extracellular matrix, but these remain to be tested. Low flow angiomatosis of the leptomeninges appears to result in a chronic hypoxic state leading to cortical atrophy and calcifications.

CLINICAL MANIFESTATIONS
The facial port-wine stain is present at birth, tends to be unilateral, and always involves the upper face and eyelid, in a distribution consistent with the ophthalmic division of the trigeminal nerve (Fig. 596-9). The capillary malformation may also be evident over the lower face, trunk, and in the mucosa of the mouth and pharynx. It is important to note that not all children with facial port-wine stain have SWS even though the genetic defect appears to be the same. In fact, the overall incidence of SWS has been reported to be 8-33% in those with a port-wine stain. Buphthalmos and glaucoma of the ipsilateral eye are common complications. The incidence of epilepsy in patients with SWS is 75-90%, and seizures develop in most patients in the 1st yr of life. They are typically focal tonic–clonic and contralateral to the side of the facial capillary malformation. The seizures may become refractory to anticonvulsants and are associated with a slowly progressive hemiparesis in many cases. Transient stroke-like episodes or visual defects persisting for several days and unrelated to seizure activity are common and probably result from thrombosis of cortical veins in the affected region. Although neurodevelopment appears to be normal in the 1st yr of life, intellectual disability or severe learning disabilities are present in at least 50% in later childhood, probably the result of intractable epilepsy and increasing cerebral atrophy.

DIAGNOSIS
MRI with contrast is the imaging modality of choice for demonstrating the leptomeningeal angioma in SWS (Fig. 596-10). White matter abnormalities are common and are thought to be a result of chronic hypoxia. Often, atrophy is noted ipsilateral to the leptomeningeal angiomatosis. Calcifications can be seen best with a head CT (Fig. 596-11).
Ophthalmologic evaluation examining for glaucoma is also necessary. Based on the involvement of the brain and the face, there are 3 types of SWS according to the Roach Scale:
1. Type I—Both facial and leptomeningeal angiomata; may have glaucoma
2. Type II—Facial angiomata alone (no central nervous system involvement); may have glaucoma
3. Type III—Isolated leptomeningeal angiomata; usually no glaucoma

**MANAGEMENT**

Management of SWS is symptomatic and multidisciplinary but not well studied by prospective studies. It is aimed at seizure control, treatment of headaches, and prevention of stroke-like episodes, as well as monitoring of glaucoma and laser therapy for the cutaneous capillary malformations. Seizures beginning in infancy are not always associated with a poor neurodevelopmental outcome. For patients with well-controlled seizures and normal or near-normal development, management consists of anticonvulsants and surveillance for complications including glaucoma, buphthalmos, and behavioral abnormalities. If the seizures are refractory to anticonvulsant therapy, especially in infancy and the 1st 1-2 yr, and arise from primarily 1 hemisphere, most medical centers advise a hemispherectomy. Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated. The facial port-wine stain is often a target of ridicule by classmates, leading to psychologic trauma. Pulsed-dye laser therapy often provides excellent clearing of the port-wine stain, particularly if it is located on the forehead.

_Bibliography is available at Expert Consult._

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**596.4 Von Hippel-Lindau Disease**

_Mustafa Sahin_

Von Hippel-Lindau disease affects many organs, including the cerebellum, spinal cord, retina, kidney, pancreas, and epididymis. Its incidence is around 1 in 36,000 newborns. It results from an autosomal-dominant mutation affecting a tumor suppressor gene, VHL. Approximately 80% of individuals with von Hippel-Lindau syndrome have an affected parent, and approximately 20% have a de novo gene mutation. Molecular testing is available and detects mutations in almost 100% of probands.

The major neurologic features of the condition include cerebellar hemangioblastomas and retinal angiomas. Patients with cerebellar hemangioblastoma present in early adult life with symptoms and signs of increased intracranial pressure. A smaller number of patients have hemangioblastoma of the spinal cord, producing abnormalities of proprioception and disturbances of gait and bladder dysfunction. A CT or MRI scan typically shows a cystic cerebellar lesion with a vascular mural nodule. Total surgical removal of the tumor is curative.

Approximately 25% of patients with cerebellar hemangioblastoma have retinal angiomas. Retinal angiomas are characterized by small masses of thin-walled capillaries that are fed by large and tortuous arterioles and venules. They are usually located in the peripheral retina so that vision is unaffected. Exudation in the region of the angiomas may lead to retinal detachment and visual loss. Retinal angiomas are treated with photocoagulation and cryocoagulation, and both have produced good results.

Cystic lesions of the kidneys, pancreas, liver, and epididymis as well as pheochromocytoma are frequently associated with von Hippel-Lindau disease. Renal carcinoma is the most common cause of death. Regular follow-up and appropriate imaging studies are necessary to identify lesions that may be treated at an early stage.

_Bibliography is available at Expert Consult._

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**596.5 Linear Nevus Syndrome**

_Mustafa Sahin_

This sporadic condition is characterized by a facial nevus and neurodevelopmental abnormalities. The nevus is located on the forehead and nose and tends to be midline in its distribution. It may be quite faint during infancy but later becomes hyperkeratotic, with a yellow-brown appearance. Two thirds of the patients with linear nevus syndrome demonstrate associated neurologic findings, including cortical dysplasia, glial hamartomas, and low-grade gliomas. Cerebral and cranial anomalies, predominantly hemimegalencephaly and enlargement of the lateral ventricles, were reported in 72% of cases. The incidence of epilepsy has been reported as high as 75% and intellectual disability as high as 60%. Focal neurologic signs including hemiparesis and homonymous hemianopia may also be seen.

_Bibliography is available at Expert Consult._

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**596.6 PHACE Syndrome**

_Mustafa Sahin_

See also Chapter 650.

The syndrome denotes posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and other cardiac defects, and eye abnormalities. It is also referred to as PHACES syndrome when ventral developmental defects, including sphenoid clefting and/or a supraumbilical raphe, are present. Large facial hemangiomas may be associated with a Dandy-Walker malformation, vascular anomalies (coarctation of aorta, aplasia or hypoplastic carotid arteries, aneurysmal carotid dilation, aberrant left subclavian artery), glaucoma, cataracts, microphthalmia, optic nerve hypoplasia, and ventral defects (skeletal clefts). The facial hemangioma is typically ipsilateral to the aortic arch. The Dandy-Walker malformation is the most common developmental abnormality of the brain. Other anomalies include hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum, and septum pellucidum. Cerebrovascular anomalies can result in acquired, progressive vessel stenosis and acute ischemic stroke. According to a case series of 29 children with PHACE syndrome, 44% had language delay, 36% gross motor delay, and 8% fine motor delay; 52% had an abnormal neurologic exam, with speech abnormalities as the most common finding. Overall, there is a female predominance. The underlying pathogenesis of PHACE syndrome remains unknown. Propranolol is starting to be used for treatment of the infantile hemangiomas associated with PHACE syndrome.

_Bibliography is available at Expert Consult._

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**596.7 Incontinentia Pigmenti**

_Mustafa Sahin_

This rare, heritable, multisystem ectodermal disorder features dermatologic, dental, and ocular abnormalities. The phenotype is produced by functional mosaicism caused by random X-inactivation of an X-linked dominant gene that is lethal in males (_IKBKG [inhibitor of kappa B kinase gamma, previously NEMO]_ gene). The paucity of affected males, the occurrence of female-to-female transmission, and an increased frequency of spontaneous abortions in carrier females support this supposition.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

This disease has 4 phases, not all of which may occur in a given patient. The 1st phase is evident at birth or in the 1st few wk of life and consists of erythematous linear streaks and plaques of vesicles (Fig. 596-12) that are most pronounced on the limbs and circumferentially...
**Bibliography**


Bibliography

Bibliography
Bibliography


on the trunk. The lesions may be confused with those of herpes simplex, bullous impetigo, or mastocytosis, but the linear configuration is unique. Histopathologically, epidermal edema and eosinophil-filled intraepidermal vesicles are present. Eosinophils also infiltrate the adjacent epidermis and dermis. Blood eosinophilia as high as 65% of the white blood cell count is common. The 1st stage generally resolves by 4 mo of age, but mild, short-lived recurrences of blisters may develop during febrile illnesses. In the 2nd phase, as blisters on the distal limbs resolve, they become dry and hyperkeratotic, forming verrucous plaques. The verrucous plaques rarely affect the trunk or face and generally involute within 6 mo. Epidermal hyperplasia, hyperkeratosis, and papillomatosis are characteristic. The 3rd or pigmentary stage is the hallmark of incontinentia pigmenti. It generally develops over weeks to months and may overlap the earlier phases, be evident at birth, or, more commonly, begin to appear in the 1st few wk of life. Hyperpigmentation is more often apparent on the trunk than the limbs and is distributed in macular whorls, reticulated patches, flecks, and linear streaks that follow Blaschko lines. The axillae and groin are invariably affected. The sites of involvement are not necessarily those of the preceding vesicular and warty lesions. The pigmented lesions, once present, persist throughout childhood. They generally begin to fade by early adolescence and often disappear by age 16 yr. Occasionally, the pigmentation remains permanently, particularly in the groin. The lesion, histopathologically, shows vacuolar degeneration of the epidermal basal cells and melanin in melanophages of the upper dermis as a result of incontinence of pigment. In the 4th stage, hairless, anhidrotic, hypopigmented patches or streaks occur as a late manifestation of incontinentia pigmenti; they may develop, however, before the hyperpigmentation of stage 3 has resolved. The lesions develop mainly on the flexor aspect of the lower legs and less often on the arms and trunk.

Approximately 80% of affected children have other defects. Alopecia, which may be scarring and patchy or diffuse, is most common on the vertex and occurs in up to 40% of patients. Hair may be lusterless, wiry, and coarse. Dental anomalies, which are present in up to 80% of patients and are persistent throughout life, consist of late dentition, hypodontia, conical teeth, and impaction. Central nervous system manifestations, including seizures, intellectual disability, hemiplegia, hemiparesis, spasticity, microcephaly, and cerebellar ataxia, are found in up to 30% of affected children. Ocular anomalies, such as neovascularization, microphthalmos, strabismus, optic nerve atrophy, cataracts, and retrolenticular masses, occur in >30% of children. Nonetheless, >90% of patients have normal vision. Less common abnormalities include dystrophy of nails (ridging, pitting) and skeletal defects.

Diagnosis of incontinentia pigmenti is made on clinical grounds, although major and minor criteria have been established to aid in diagnosis. Wood's lamp examination may be useful in older children and adolescents to highlight pigmentary abnormalities. Clinical molecular testing is available, and in 80% of the affected patients a deletion that removes exons 4 through 10 of IKBKG gene can be detected. Differential diagnosis includes hypomelanosis of Ito, which presents with similar skin manifestations and is often associated with chromosomal mosaicism.

MANAGEMENT
The choice of investigative studies and the plan of management depend on the occurrence of particular noncutaneous abnormalities since the skin lesions are benign. The high incidence of associated major anomalies warrants genetic counseling.

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


Movement disorders are characterized by abnormal or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. Most movement disorders in children are characterized by involuntary movements. These involuntary movements can represent the sole disease manifestation, or they may be one of many signs and symptoms.

Evaluation of movement disorders begins with a comprehensive history and careful neurologic examination. It is often difficult for children and caregivers to describe abnormal movements, which makes observation of the movements by the clinician an essential component of the evaluation. If the movements are not apparent at the time of the examination, video examples from home or school can be invaluable. With the increasing availability of high quality video capability on cellular phones, obtaining a short video is feasible for most families. Resources are available to guide families in gathering useful video data.

There is no specific diagnostic test to differentiate among movement disorders. The category of movement assists in localizing the pathologic process, whereas the onset, age, and degree of abnormal motor activity and associated neurologic findings help organize the investigation.

When considering the type of movement disorder, the following questions concerning the history and examination of the movement are helpful.

- What is the distribution of the movements across body parts?
- Are the movements symmetric?
- What is the speed of the involuntary movements? Are they rapid and fast or slow and sustained?
- When do the movements occur? Are they present at rest? Are they present with maintained posture or with voluntary actions?
- Are the movements seen in relation to certain postures or body positions?
- Do the abnormal movements occur only with specific tasks?
- Can the child voluntarily suppress the movements, even for a short time?
- Are the movements stereotyped?
- Are the movements rhythmic?
- What is the temporal pattern of the movements? Are they continuous or intermittent? Do they occur in discrete episodes?
- Are the involuntary movements preceded by an urge to make the movement?
- Do the movements persist during sleep?
- Are the movements associated with impairment of motor function?
- What factors aggravated or alleviate the movements?
The first decision to be made is whether the movement disorder is "hyperkinetic" (characterized by excessive and involuntary movements) or "hypokinetic" (characterized by slow voluntary movements and a general paucity of movement). Hyperkinetic movement disorders are much more common than hypokinetic disorders in children. Once the category of movement disorder is recognized, etiology can be considered. Clinical history, including birth history, medication/toxin exposure, trauma, infections, family history, progression of the involuntary movements, developmental progress, and behavior should be explored as the underlying cause is established. Table 597-1 lists types and clinical characteristics of selected hyperkinetic movement disorders.

597.1 Ataxias

Ataxia is the inability to make smooth, accurate, and coordinated movements, usually because of a dysfunction of the cerebellum, its inputs or outputs, sensory pathways in the posterior columns of the spinal cord, or a combination of these. Ataxias may be generalized or primarily affect gait or the hands and arms or trunk; they may be acute or chronic, acquired or genetic (Tables 597.2 to 597.5). Signs and symptoms of ataxia include clumsiness, difficulty walking or sitting, falling to 1 side, slurred speech, hypotonia, intention tremor, dizziness, and delayed motor development. Genetic or chronic causes of cerebellar ataxia are often characterized by a long duration of symptoms, a positive family history, muscle weakness and abnormal gait, abnormal tone and strength, abnormal deep tendon reflexes, pes cavus, and sensory defects. Distinguishing ataxia from vestibular dysfunction may be difficult; however, labyrinth disorders are often characterized by severe vertigo, nausea and vomiting, position-induced vertigo, and a severe sense of unsteadiness.

Congenital anomalies of the posterior fossa, including the Dandy-Walker malformation, Chiari malformation, and encephalocoele, are prominently associated with ataxia because of their destruction or replacement of the cerebellum (see Chapter 591.9). MRI is the method of choice for investigating congenital abnormalities of the cerebellum, vermis, and related structures. Agenesis of the cerebellar vermis presents in infancy with generalized hypotonia and decreased deep-tendon reflexes. Delayed motor milestones and truncal ataxia are typical. Joubert syndrome and related disorders are autosomal recessive disorders marked by developmental delay, hypotonia, abnormal eye movements, abnormal respirations, and a distinctive malformation of the cerebellum and brainstem that manifests as the "molar tooth sign" on MRI. Mutations in more than 21 different genes are associated with Joubert syndrome, but only approximately 50% of cases have a demonstrated causal mutation (see Chapter 591).

The major infectious causes of ataxia include cerebellar abscess, acute labyrinthitis, and acute cerebellar ataxia. Acute cerebellar ataxia occurs primarily in children 1-3 yr of age and is a diagnosis of exclusion. The condition often follows a viral illness, such as varicella virus, coxsackievirus, or echovirus infection by 2-3 wk and is thought to represent an autoimmune response to the viral agent affecting the cerebellum (see Chapters 250, 253, and 603). The onset is sudden, and the truncal ataxia can be so severe that the child is unable to stand or sit. Vomiting may occur initially, but fever and nuchal rigidity are absent. Horizontal nystagmus is evident in approximately 50% of cases and, if the child is able to speak, dysarthria may be impressive. Examination of the cerebrospinal fluid is typically normal at the onset of ataxia but a mild lymphocytic pleocytosis (10-30/mm³) is not unusual. Later in the course, the cerebrospinal fluid protein undergoes a moderate elevation. The ataxia begins to improve in a few weeks but may persist for as long as 3 mo and rarely longer than that. The incidence of acute cerebellar ataxia appears to have declined with increased rates of vaccination against varicella. The prognosis for complete recovery is excellent; a small number have long-term sequelae, including behavioral and speech disorders as well as ataxia and incoordination. Acute cerebellitis in contrast is a more severe form of cerebellar ataxia demonstrating abnormal MRI scans, more severe symptoms, and a poorer long-term prognosis. Infectious agents include Epstein-Barr virus, mycoplasma, mumps, and influenza virus, although in many the etiology is unknown; autoimmune cerebellitis may represent some of these unknown cases. Patients may present with ataxia, increased intracranial pressure from obstructive hydrocephalus, headache and fever. Acute labyrinthitis may be difficult to differentiate from acute cerebellar ataxia in a toddler. The condition is associated with middle-ear infections and presents with intense vertigo, vomiting, and abnormalities in labyrinthine function.

Toxic causes of ataxia include alcohol, thallium (which is used occasionally in homes as a pesticide), and the anticonvulsants, particularly phenytoin and carbamazepine when serum levels exceed the usual therapeutic range.

Brain tumors (see Chapter 497), including tumors of the cerebellum and frontal lobe, as well as peripheral nervous system neuroblastoma, may present with ataxia. Cerebellar tumors cause ataxia because of direct disruption of cerebellar function or indirectly because of increased intracranial pressure from compression of the fourth ventricle. Frontal lobe tumors may cause ataxia as a consequence of destruction of the association fibers connecting the frontal lobe with the cerebellum or because of increased intracranial pressure. Neuroblastoma (see Chapter 498) may be associated with a paraneoplastic encephalopathy characterized by progressive ataxia, myoclonic jerks,
### Table 597-2  Selected Causes of Ataxia in Childhood

**CONGENITAL**
- Agenesis of vermis of the cerebellum
- Aplasia or dysplasia of the cerebellum
- Basilar impression
- Cerebellar dysplasia with microgyria, macrogyria, or agyria
- Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
- Chiari malformation
- Dandy-Walker syndrome
- Encephalocoele
- Hydrocephalus (progressive)
- Hypoplasia of the cerebellum

**DEGENERATIVE AND/OR GENETIC**
- Acute intermittent cerebellar ataxia
- Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
- Ataxia-telangiectasia
- Biemond posterior column ataxia
- Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
- Cockayne syndrome
- Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
- Familial ataxia with macular degeneration
- Friedreich ataxia
- Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
- Hereditary cerebellar ataxia with myotonia and cataracts
- Hypertrophic interstitial neuritis
- Marie ataxia
- Marinesco-Sjögren syndrome
- Multiple-system atrophy
- Ramsay Hunt syndrome (myoclonic seizures and ataxia)
- Roussy-Lévy disease
- Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
- Vanishing white matter syndrome

**ENDOCRINOLOGIC**
- Acquired hypothyroidism
- Cretinism

**INFECTIOUS, POSTINFECTIOUS, INFLAMMATORY**
- Acute cerebellar ataxia
- Acute disseminated encephalomyelitis
- Autoimmune (anti-glutamic acid decarboxylase, anti-γ-aminobutyric acid, receptor antibodies)
- Cerebellar abscess
- Cerebellitis
- Coxsackievirus
- Diphtheria
- Echovirus
- Fisher syndrome
- Infectious mononucleosis (Epstein-Barr virus infection)
- Infectious polyneuropathy
- Japanese B encephalitis
- Mumps encephalitis
- Mycoplasma pneumonia
- Paraneoplastic (oposconus-myoclonus-ataxia syndrome)
- Pertussis
- Polio
- Postbacterial meningitis
- Rueboela
- Tuberculosis
- Typhoid
- Varicella

**METABOLIC**
- Abetalipoproteinemia
- Argininosuccinic aciduria
- Ataxia with vitamin E deficiency (AVED)
- Congenital disorders of glycosylation
- GM1 gangliosidosis (late)
- Hartnup disease
- Hyperalaninemia
- Hyperammonemia I and II (urea cycle defects)
- Hypoglycemia
- Kearns-Sayre syndrome
- Leigh disease
- Maple syrup urine disease (intermittent)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Metachromatic leukodystrophy
- Mitochondrial complex defects (I, III, IV)
- Multiple carboxylase deficiency (biotinidase deficiency)
- Neuronal ceroid-lipofuscinosis
- Neuropathy, ataxia, retinitis pigmentosa (NARP)
- Niemann-Pick disease (late infantile)
- 5-Oxoprolinuria
- Pyruvate decarboxylase deficiency
- Refsum disease
- Sialidosis
- Triose-phosphate isomerase deficiency
- Tryptophanuria
- Wernicke encephalopathy

**NEOPLASTIC**
- Frontal lobe tumors
- Hemispheric cerebellar tumors
- Midline cerebellar tumors
- Neuroblastoma
- Pontine tumors (primarily gliomas)
- Spinal cord tumors

**PRIMARY PSYCHOGENIC**
- Conversion reaction

**TOXIC**
- Alcohol
- Benzodiazepines
- Carbamazepine
- Clonazepam
- Lead encephalopathy
- Neuroblastoma
- Phenobarbital
- Phenytin
- Primidone
- Tic paralysis poisoning

**TRAUMATIC**
- Acute cerebellar edema
- Acute frontal lobe edema

**VASCULAR**
- Angioblastoma of cerebellum
- Basilar migraine
- Cerebellar embolism
- Cerebellar hemorrhage
- Cerebellar thrombosis
- Posterior cerebellar artery disease
- Vasculitis
- von Hippel-Lindau disease

### Table 597-3 Treatable Causes of Inherited Ataxia

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>METABOLIC ABNORMALITY</th>
<th>DISTINGUISHING CLINICAL FEATURES</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Demyelination</td>
<td>Positive MRI findings</td>
<td>Steroids, IVIG, rituximab</td>
</tr>
<tr>
<td>Ataxia with vitamin E deficiency</td>
<td>Mutation in α-tocopherol transfer protein</td>
<td>Ataxia, areflexia, retinopathy</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Bassen-Kornzweig syndrome</td>
<td>Abetalipoproteinemia</td>
<td>Acanthocytosis, retinitis pigmentosa, fat malabsorption</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>Tryptophan malabsorption</td>
<td>Pellagra rash, intermittent ataxia</td>
<td>Niacin</td>
</tr>
<tr>
<td>Familial episodic ataxia type 1 and type 2</td>
<td>Mutations in potassium channel (KCNA1) and α1A voltage-gated calcium channel, respectively</td>
<td>Episodic attacks, worse with pregnancy or birth control pills</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency</td>
<td>Biotinidase deficiency</td>
<td>Alopecia, recurrent infections, variable organic aciduria</td>
<td>Biotin</td>
</tr>
<tr>
<td>Mitochondrial complex defects</td>
<td>Complexes I, III, IV</td>
<td>Encephalomyelopathy</td>
<td>Possibly riboflavin, CoQ10, dichloroacetate</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus-ataxia syndrome</td>
<td>Paraneoplastic or spontaneous autoimmune</td>
<td>Underlying neuroblastoma or autoantibodies</td>
<td>Steroids, IVIG, rituximab</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase deficiency</td>
<td>Block in E-M and Krebs cycle interface</td>
<td>Lactic acidosis, ataxia</td>
<td>Ketogenic diet, possibly dichloroacetate</td>
</tr>
<tr>
<td>Refsum disease</td>
<td>Phytanic acid, α-hydroxylase</td>
<td>Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis</td>
<td>Dietary restriction of phytanic acid</td>
</tr>
<tr>
<td>Urea cycle defects</td>
<td>Urea cycle enzymes</td>
<td>Hyperammonemia</td>
<td>Protein restriction, arginine, benzoate, α-ketoacids</td>
</tr>
</tbody>
</table>

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.


### Table 597-4 Autosomal-Recessive Cerebellar Ataxias

<table>
<thead>
<tr>
<th>ATAXIA</th>
<th>CHROMOSOME</th>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>MECHANISM</th>
<th>AGE OF ONSET (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedreich ataxia</td>
<td>9q13</td>
<td>X25</td>
<td>Frataxin</td>
<td>GAA repeat</td>
<td>2-51</td>
</tr>
<tr>
<td>Friedreich ataxia 2</td>
<td>9p23-p11</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>5-20</td>
</tr>
<tr>
<td>AVED</td>
<td>8q13</td>
<td>TTP1</td>
<td>TTPA</td>
<td>Missense mutation, deletion, insertion</td>
<td>2-52</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>11q22.3</td>
<td>ATM</td>
<td>ATM</td>
<td>Missense and deletion mutations</td>
<td>Infancy</td>
</tr>
<tr>
<td>ATLD</td>
<td>11q21</td>
<td>hMRE11</td>
<td>MRE11A</td>
<td>Missense and deletion mutations</td>
<td>9-48 mo</td>
</tr>
<tr>
<td>Ataxia-ocular apraxia 1</td>
<td>9p13.3</td>
<td>APTX</td>
<td>Aprataxin</td>
<td>Frameshift, missense, nonsense mutations</td>
<td>2-18</td>
</tr>
<tr>
<td>SCAR1</td>
<td>9q34</td>
<td>SETX</td>
<td>Senataxin</td>
<td>Frameshift, missense, nonsense mutations</td>
<td>9-22</td>
</tr>
<tr>
<td>SCAR2</td>
<td>9q34-pter</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Congenital</td>
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<td>SCAR3</td>
<td>6p23-p21</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>3-52</td>
</tr>
<tr>
<td>SCAR4</td>
<td>1p36</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>23-39</td>
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<td>SCAR5</td>
<td>15q24-q26</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>1-10</td>
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<tr>
<td>SCAR6</td>
<td>20q11-q13</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Infancy</td>
</tr>
<tr>
<td>SCAR7</td>
<td>11p15</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Childhood</td>
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<tr>
<td>SCAR8</td>
<td>11p15</td>
<td>SYNE1</td>
<td>SYNE1</td>
<td>Splice site mutation, nonsense mutations</td>
<td>17-46</td>
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</table>

*Continued*
### Table 597-4  Autosomal-Recessive Cerebellar Ataxias—cont’d

<table>
<thead>
<tr>
<th>ATAXIA</th>
<th>CHROMOSOME</th>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>MECHANISM</th>
<th>AGE OF ONSET (yr)</th>
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</thead>
<tbody>
<tr>
<td>SCAR9</td>
<td>1q41</td>
<td>ADCK3</td>
<td>ADCK3</td>
<td>Splice site mutation, missense, nonsense mutations</td>
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</tr>
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<td>Ataxia, Cayman type</td>
<td>19q13.3</td>
<td>ATCAY</td>
<td>Caytaxin</td>
<td>Missense mutation</td>
<td>Birth</td>
</tr>
<tr>
<td>IOSCA</td>
<td>10q24</td>
<td>C10orf2</td>
<td>Twinkle</td>
<td>Missense, silent mutations</td>
<td>9-24 mo</td>
</tr>
<tr>
<td>Progressive myoclonic epilepsy</td>
<td>21q22.3</td>
<td>CST6</td>
<td>Cystatin B</td>
<td>5’ dodecamer repeat</td>
<td>6-13</td>
</tr>
<tr>
<td>ARSACS</td>
<td>13q12</td>
<td>SACS</td>
<td>Sacsin</td>
<td>Frameshift and nonsense mutations</td>
<td>1–20</td>
</tr>
<tr>
<td>Congenital disorders of glycosylation</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Birth</td>
<td></td>
</tr>
</tbody>
</table>

ARSACS, autosomal-recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; IOSCA, infantile-onset spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal-recessive.


### Table 597-5  Autosomal-Dominant Cerebellar Ataxias

<table>
<thead>
<tr>
<th>ATAXIA</th>
<th>CHROMOSOME</th>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>MECHANISM</th>
<th>AGE OF ONSET (yr)</th>
<th>NORMAL REPEAT</th>
<th>EXPANDED REPEAT</th>
<th>DURATION OF EPISODES</th>
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<tbody>
<tr>
<td>POLYGLUTAMINE EXPANSION</td>
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<td>SCA1</td>
<td>6p23</td>
<td>SCA1</td>
<td>Ataxin-1</td>
<td>CAG repeat</td>
<td>6-60</td>
<td>6-44*</td>
<td>39-82*</td>
<td></td>
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<tr>
<td>SCA2</td>
<td>12q24</td>
<td>SCA2</td>
<td>Ataxin-2</td>
<td>CAG repeat</td>
<td>2-65</td>
<td>15-24</td>
<td>35-59</td>
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</tr>
<tr>
<td>SCA3/MJD</td>
<td>14q24.3-q31</td>
<td>MJD1</td>
<td>Ataxin-3</td>
<td>CAG repeat</td>
<td>11-70</td>
<td>13-47*</td>
<td>45-84*</td>
<td></td>
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<tr>
<td>SCA6</td>
<td>19q13</td>
<td>CACNA1A</td>
<td>CACNA1A</td>
<td>CAG repeat</td>
<td>16-73</td>
<td>4-20</td>
<td>21-33</td>
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<tr>
<td>SCA17</td>
<td>6q27</td>
<td>SCA17</td>
<td>TBP</td>
<td>CAG repeat</td>
<td>3-48</td>
<td>25-42</td>
<td>45-66</td>
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<tr>
<td>DRPLA</td>
<td>12p13.31</td>
<td>DRPLA</td>
<td>Atrophin-1</td>
<td>CAG repeat</td>
<td>4-55 mo</td>
<td>7-34</td>
<td>53-93</td>
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<td>NONCODING EXPANSION</td>
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<tr>
<td>SCA8</td>
<td>13q21</td>
<td>SCA8</td>
<td>SCA8 RNA</td>
<td>CTG repeat in 3’ UTR</td>
<td>18-72</td>
<td>2.91*</td>
<td>110-155*</td>
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<tr>
<td>SCA10</td>
<td>22q13</td>
<td>SCA10</td>
<td>Ataxin-10</td>
<td>ATTCT repeat in intron 9</td>
<td>14-45</td>
<td>10-29</td>
<td>750-4500</td>
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<tr>
<td>SCA12</td>
<td>5q31-q33</td>
<td>SCA12</td>
<td>P2R2B</td>
<td>CAG repeat in 5’ UTR</td>
<td>8-55</td>
<td>7-32</td>
<td>55-78</td>
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<tr>
<td>SCA31</td>
<td>16q22.1</td>
<td>BEAN/TK2</td>
<td>BEAN/TK2</td>
<td>TGGAA repeat insertion in intron of BEAN and TK</td>
<td>45-72</td>
<td>Rarely (0.23%)</td>
<td>2.5-3.8 kb</td>
<td>1.5-2.0 kb</td>
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<tr>
<td>OTHER MUTATIONS</td>
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<td>SCA14</td>
<td>19q13.4</td>
<td>PKC-γ</td>
<td>PKC-γ</td>
<td>Missense mutation</td>
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<tr>
<td>SCA27</td>
<td>13q34</td>
<td>FGFI14</td>
<td>FGFI14</td>
<td>Fibroblast growth factor deficiency</td>
<td>15-20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA5</td>
<td>11p11-q11</td>
<td>SPTBN2</td>
<td>β-3 spectrin</td>
<td>Deletion, missense mutations</td>
<td>10-68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA11</td>
<td>15q14-q21.3</td>
<td>TTBK2</td>
<td>TTBK2</td>
<td>Truncation mutation</td>
<td>15-43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA13</td>
<td>19q13.3-q13.4</td>
<td>KCNC3</td>
<td>KCNC3</td>
<td>Missense mutations</td>
<td>&lt;1-60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA15</td>
<td>3p24.2-3pter</td>
<td>ITPR1</td>
<td>ITPR1</td>
<td>Deletion, missense mutations</td>
<td>Child–adult</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA28</td>
<td>18p11.22-q11.2</td>
<td>AFG3L2</td>
<td>AFG3L2</td>
<td>Missense mutations</td>
<td>12-36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and opsinclonus (nurhythmic, conjugate horizontal and vertical oscillations of the eyes).

Several metabolic disorders are characterized by ataxia, including abetalipoproteinemia, arginosuccinic aciduria, and Hartnup disease. Abetalipoproteinemia (Bassen-Kornzweig disease) begins in childhood with steatorrhea and failure to thrive (see Chapters 86.3 and 600). A blood smear shows acanthocytosis. Serum chemistries reveal decreased levels of cholesterol and triglycerides; serum β-lipoproteins are absent. Neurologic signs become evident by late childhood and consist of ataxia, retinitis pigmentosa, peripheral neuritis, abnormalities of position and vibration sense, muscle weakness, and intellectual disability. Vitamin E is undetectable in the serum of patients with neurologic symptoms.

Degenerative diseases of the central nervous system represent an important group of ataxic disorders of childhood because of the genetic consequences and poor prognosis. Ataxia-telangiectasia, an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded by ataxia beginning at approximately age 2 yr and progressing to loss of ambulation by adolescence. Ataxia-telangiectasia results from infection or tumor dissemination. The onset of ataxia is somewhat later than in ataxia-telangiectasia, particularly of chromosome 14, and elevated levels of α-fetoprotein. Death results from infection or tumor dissemination.

Friedreich ataxia is inherited as an autosomal-recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, the pyramidal tracts, and the cerebellum and medulla. The majority of patients are homozygous for a GAA repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Mutations cause oxidative injury associated with excessive iron deposits in mitochondria. The onset of ataxia is somewhat later than in ataxia-telangiectasia, but usually occurs before age 10 yr. The ataxia is slowly progressive and involves the lower extremities to a greater degree than the upper extremities. The Romberg test result is positive; the deep-tendon reflexes are absent (particularly at the ankle), and the plantar response is typically extensor (Babinski sign). Patients develop

<table>
<thead>
<tr>
<th>ATAXIA</th>
<th>CHROMOSOME</th>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>MECHANISM</th>
<th>AGE OF ONSET (yr)</th>
<th>NORMAL REPEAT</th>
<th>EXPANDED REPEAT</th>
<th>DURATION OF EPISODES</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUTATION UNKNOWN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA4</td>
<td>16q22</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>19-59</td>
<td>12-25</td>
<td>10-45</td>
<td>19-64</td>
</tr>
<tr>
<td>SCA18/SMNA</td>
<td>7q31-q32</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>6-30</td>
<td>10-46</td>
<td>43-56</td>
<td>1.5-39</td>
</tr>
<tr>
<td>SCA19</td>
<td>1p21-q21</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>26-60</td>
<td>45-76</td>
<td>Early childhood to early 20s</td>
<td></td>
</tr>
<tr>
<td>SCA20</td>
<td>11</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA21</td>
<td>7p21.3-p15.1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA22</td>
<td>1p21-q23</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA23</td>
<td>20p13-p12.2</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA25</td>
<td>2p</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA26</td>
<td>19q13.3</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA30</td>
<td>7q31-q32</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAX1</td>
<td>12p13</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAR</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPISODIC ATAXIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA1</td>
<td>12p13</td>
<td>EA1</td>
<td>KCNA1</td>
<td>Channelopathy</td>
<td>Early childhood</td>
<td>Hours to days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA2/FHM</td>
<td>19p13</td>
<td>CACNA1A</td>
<td>CACNA1A</td>
<td>Channelopathy: missense and nonsense mutations</td>
<td>Early childhood</td>
<td>Hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA3</td>
<td>1q42</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA4</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA5</td>
<td>2q22-q23</td>
<td>CACNB4</td>
<td>CACNB4</td>
<td>Channelopathy: missense and nonsense mutations</td>
<td>Juvenile</td>
<td>Hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA6</td>
<td>5p13</td>
<td>SLC1A3</td>
<td>EAAT1</td>
<td>Missense mutation</td>
<td>5</td>
<td>Hours to days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA7</td>
<td>19q13</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td>Hours to days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Some overlap of pathogenic and non-pathogenic repeat length.

DRPLA, dentatorubral-pallidoluysian atrophy; EA, episodic ataxia; FHM, familial hemiplegic migraine; MJD, Machado-Joseph disease; SAX, spastic ataxia; SCA, spinocerebellar ataxia; SMNA, sensorimotor neuropathy with ataxia; SPAR, spastic paraplegia, ataxia, and mental retardation; TBP, TATA-binding protein, UTR, untranslated region.

Chorea, meaning “dance-like” in Greek, refers to rapid, chaotic movements that seem to flow from 1 body part to another. Affected individuals exhibit motor impersistence, with difficulty keeping the tongue protruded (“darting tongue”) or maintaining grip (“milkmaid grip”). Chorea tends to occur both at rest and with action. Patients often attempt to incorporate the involuntary movements into more purposeful movements, making them appear fidgety. Chorea increases with stress and disappears in sleep. Chorea can be divided into primary (i.e., disorders in which chorea is the dominant symptom and the etiology is presumed to be genetic) and secondary forms, with the vast majority of pediatric cases falling into the latter category (Tables 597-6 and 597-7).

Sydenham chorea (St. Vitus dance) is the most common acquired chorea of childhood. It occurs in 10–20% of patients with acute rheumatic fever, typically weeks to months after a group A β-hemolytic streptococcal infection (see Chapter 183.1). Peak incidence is at age 8–9 yr, with a female predominance of 2:1. There is evidence that group A β-hemolytic streptococci promote the generation of cross-reactive or polyreactive antibodies through molecular mimicry between streptococcal and host antigens. Specifically, antibodies against the N-acetyl-β-D-glucosamine epitope (GlcNAc) of streptococcal group A carbohydrate target intracellular β-tubulin and extracellular lysoganglioside GM1 in human caudate-putamen preparations. These antibodies are also capable of directing calcium/calmodulin-dependent protein kinase II activation, which may cause the neurologic manifestations of Sydenham chorea by increasing dopamine release into the synapse.

The clinical hallmarks of Sydenham chorea are chorea, hypotonia, and emotional lability. Onset of the chorea is usually insidious but may be abrupt. Most patients have generalized chorea but the majority have asymmetric manifestations and up to 20% have hemichorea. Hypotonia manifests with the “pronator sign” (arms and palms turn outward when held overhead) and the “choreic hand” (spooning of the extended hand by flexion of the wrist and extension of the fingers). When chorea and hypotonia are severe, the child may be incapable of feeding, dressing, or walking without assistance. Speech is often involved, sometimes to the point of being unintelligible. Periods of uncontrollable crying and extreme mood swings are characteristic and may precede the onset of the movement disorder.
<table>
<thead>
<tr>
<th>Gene, Location</th>
<th>Protein Product</th>
<th>Usual Age at Onset (yr)</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL2*</td>
<td>JPH3, 16q</td>
<td>20-40</td>
<td>Huntington disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity</td>
</tr>
<tr>
<td>SCA17</td>
<td>TBP, 6q</td>
<td>10-30</td>
<td>Cerebellar ataxia, chorea, dystonia, hyperreflexia, cognitive decline</td>
</tr>
<tr>
<td>DRPLA</td>
<td>DRPLA, 12p</td>
<td>About 20</td>
<td>Variable phenotypic picture including chorea, ataxia, seizures, psychiatric disturbances, dementia; more common in Japan than in Europe or United States</td>
</tr>
<tr>
<td>SCA3/MJD</td>
<td>MJD, 14q</td>
<td>35-40</td>
<td>Wide phenotypic variability with cerebellar ataxia, protruded eyes, chorea, dystonia, parkinsonian features, neuropathy, pyramidal tract features</td>
</tr>
<tr>
<td>SCA2</td>
<td>Ataxin-2, 12q</td>
<td>30-35</td>
<td>Cerebellar ataxia, chorea, markedly reduced velocity of saccadic eye movements, hyperreflexia</td>
</tr>
<tr>
<td>Chorea-</td>
<td>VPS13A</td>
<td>20-50</td>
<td>Orofacial self-mutilation, dystonia, neuropathy, myopathy, seizures, acanthocytosis</td>
</tr>
<tr>
<td>acanthocytosis</td>
<td>(formerly CHAC, 9q)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLeod syndrome</td>
<td>XK, Xp</td>
<td>40-70</td>
<td>Dystonia, neuropathy, myopathy, cardiomyopathy, seizures, acanthocytosis, raised creatine kinase, weak expression of Kell antigen</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>FTL, 19q</td>
<td>20-55</td>
<td>Chorea, dystonia, parkinsonian features; usually reduced serum ferritin; MR abnormalities with cyst formation and increased T2 signal in globus pallidus and putamen</td>
</tr>
<tr>
<td>AT and ATLD</td>
<td>ATM, 11q (AT) MRE11, 11q (ATLD)</td>
<td>Childhood</td>
<td>Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea, dystonia, and myoclonus</td>
</tr>
<tr>
<td></td>
<td>ATM (AT) MRE11 (ATLD)</td>
<td></td>
<td>In AT: oculocutaneous telangiectasias; predisposition to malignancies, IgA and IgG deficiency, high α-fetoprotein in serum and high concentrations of carcinoembryonic antigen</td>
</tr>
<tr>
<td>AOA 1 and 2</td>
<td>APTX, 9p (AOA 1) SETX, 9q (AOA 2)</td>
<td>Childhood or adolescence (later onset in AOA 2)</td>
<td>Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea and dystonia; ataxia with oculomotor apraxia type 1: hypoalbuminemia and hypercholesterolemia; ataxia with oculomotor apraxia type 2: raised α-fetoprotein in serum</td>
</tr>
<tr>
<td>Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)</td>
<td>PANK2, 20p</td>
<td>Childhood, but also adult-onset subtype</td>
<td>Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, “eye of the tiger” sign (hyperintense area within the hypointense area); sometimes acanthocytosis, abnormal cytosomes in lymphocytes</td>
</tr>
</tbody>
</table>

Continued
Sydenham chorea is a clinical diagnosis; a combination of acute and convalescent serum antistreptolysin O titers may help to confirm an acute streptococcal infection. Negative titers do not exclude the diagnosis. All patients with Sydenham chorea should be evaluated for carditis and started on long-term antibiotic prophylaxis (e.g., penicillin G benzathine 1.2 million units IM every 4 wk or penicillin V 250 mg PO twice daily) to decrease the risk of rheumatic heart disease with recurrence. For patients with chorea that is impairing, treatment options include valproate, carbamazepine, and dopamine receptor antagonists. Historically, there have been conflicting data regarding the efficacy of prednisone, intravenous immunoglobulin, and other immunomodulatory agents in Sydenham chorea, making it difficult to recommend their routine use. A more recent randomized, double-blinded study of 37 children with Sydenham chorea compared high-dose prednisone (2 mg/kg/day, max: 60 mg) for 4 wk vs a placebo and found that steroids significantly reduced time to remission (54.3 days vs 119.9 days in controls). There is no evidence that treatment with prednisone alters the recurrence rate or long-term outcome.

Sydenham chorea usually resolves spontaneously within 6-9 mo, although it can persist for up to 2 yr and, in rare cases, can remain a lifelong condition. Relapse in the 1st few yr is relatively common, occurring in 37.9% of patients in 1 series. Remote recurrence of chorea is rare, but may be provoked by streptococcal infections, pregnancy (chorea gravidarum), or oral contraceptive use.

Although much rarer than Sydenham chorea, systemic lupus erythematosus (see Chapter 158) is a well-known cause of chorea in children. In some cases, chorea may be the presenting sign of systemic lupus erythematosus. A recent retrospective study of a large pediatric lupus cohort examined the prevalence of antiphospholipid antibodies and evaluated their association with neuropsychiatric symptoms. There was a significant association between a persistently positive lupus anticoagulant and chorea (p = 0.02); however, only 2 of the 137 patients in the cohort had chorea. Regardless, a child with chorea of unknown cause should be investigated for the presence of antiphospholipid antibodies.

Additional causes of secondary chorea include metabolic (hyperthyroidism, hypoparathyroidism), infectious (Lyme disease), immune-mediated (systemic lupus erythematosus; anti–N-methyl-D-aspartate receptor antibody syndrome), vascular (stroke, moyamoya disease), heredodegenerative disorders (Wilson disease), and drugs (Table 597-8). Although chorea is a hallmark of Huntington disease in adults, children who develop Huntington disease tend to present with rigidity and bradykinesia (Westphal variant) or dystonia rather than chorea.

Athetosis is characterized by slow, continuous, writhing movements that repeatedly involve the same body part(s), usually the distal

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### Table 597-7 Genetic Chorae—cont’d

<table>
<thead>
<tr>
<th>MODE OF INHERITANCE</th>
<th>GENE, LOCATION</th>
<th>PROTEIN PRODUCT</th>
<th>USUAL AGE AT ONSET (yr)</th>
<th>CLINICAL SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>X-linked, recessive</td>
<td>HPRT, Xq</td>
<td>Hypoxanthine-guanine phosphoribosyltransferase</td>
<td>Childhood</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>AR</td>
<td>ATP7B, 13q</td>
<td>Copper transporting P-type adenosine triphosphatase (ATPase)</td>
<td>&lt;40</td>
</tr>
<tr>
<td>PKC syndrome and ICCA syndrome</td>
<td>AD</td>
<td>Unknown, 16p</td>
<td>Unknown</td>
<td>&lt;1-40</td>
</tr>
<tr>
<td>Benign hereditary chorea</td>
<td>AD</td>
<td>TITF-1, 14q; other</td>
<td>Thyroid transcription factor 1</td>
<td>Childhood</td>
</tr>
</tbody>
</table>

*HD1, HDL3, and HDL4 are very rare conditions (only 1 family known) and therefore not included in the table.

1. Disorders based on expanded CAG repeats (HDL2 based on CAG/CTG repeats; SCA 17 based on CAG/CAA repeats); age of symptom onset inversely related to repeat size.

2. AD, autosomal dominant; AOA, ataxia with oculomotor apraxia (types 1 or 2); AR, autosomal recessive; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia–like disorder; DRPLA, dentatorubropallidoluysian atrophy; ICCA, infantile convulsions and paroxysmal choreoathetosis syndrome; MJD, Machado-Joseph disease; PKC, paroxysmal kinesigenic choreoathetosis; SCA, spinocerebellar ataxia (types 2, 3, or 17).


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### Table 597-8 Drugs That Can Induce Chorea

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>MODALITY</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine receptor blocking agents (upon withdrawal or as a tardive syndrome)</td>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Butyrophenones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzamides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiparkinsonian drugs</td>
<td>L-DOPA</td>
<td></td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>Amphetamines</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Cinnarizine</td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids/oral contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dystonia is a disorder of movement characterized by sustained muscle contraction, frequently causing twisting and repetitive movements or abnormal postures. Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 597-10 and 597-11).

INHERITED PRIMARY DYSTONIAS

Primary generalized dystonia, also referred to as primary torsion dystonia or dystonia musculorum deformans, is caused by a group of genetic disorders with onset in childhood. One form, which occurs more commonly in the Ashkenazi Jewish population, is caused by a dominant mutation in the DYT1 gene coding for the adenosine

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597.3 Dystonia

Erika F. Augustine and Jonathan W. Mink

Dystonia is a disorder of movement characterized by sustained muscle contraction, frequently causing twisting and repetitive movements or abnormal postures. Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 597-10 and 597-11).
### Causes of Dystonia in Childhood

<table>
<thead>
<tr>
<th>Static Injury/Structural Disorders</th>
<th>Hereditary/Degenerative Disorders</th>
<th>Metabolic Disease</th>
<th>Drugs/Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>DYT1 (9q34, encodes torsinA)</td>
<td>Glutaric aciduria types 1 and 2</td>
<td>Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)</td>
</tr>
<tr>
<td>Hypoxic-ischemic injury</td>
<td>DYT2 (autosomal-recessive)</td>
<td>Acyl-coenzyme A (CoA) dehydrogenase deficiencies</td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Kernicterus</td>
<td>DYT3 (X-linked dystonia-parkinsonism syndrome of Lubag–Xq13)</td>
<td>Dopa-responsive dystonia (tyrosine hydroxylase deficiency, guanosine triphosphate [GTP] cyclodrolase 1 deficiency, DYT5)</td>
<td>Stimulants (amphetamine, cocaine, ergot alkaloids)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>DYT4</td>
<td>Dopamine agonist-responsive dystonia (aromatic l-amino acid decarboxylase deficiency, aminolevulinic acid dehydrase [ALAD])</td>
<td>Anticonvulsants (carbamazepine, phenytoin)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>DYT5 (14q22.1-2, encodes GTP cyclodrolase 1, leading to dopa-responsive dystonia or Segawa disease)</td>
<td>Biotin responsive basal ganglia disease</td>
<td>Thallium</td>
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<tr>
<td>Tumors</td>
<td>DYT6 (8p21-q22)</td>
<td>Mitochondrial disorders</td>
<td>Manganese</td>
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<td>Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)</td>
<td>DYT7 (18p)</td>
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<td>Congenital malformations</td>
<td>DYT8 (2q33-q35, causing paroxysmal nonkinesigenic choreoathetosis [PNKC])</td>
<td>Vitamin E deficiency</td>
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<td>DYT9 (1p, causing paroxysmal nonkinesigenic dyskinesia [PNKD] and spasticity)</td>
<td>Homocystinuria</td>
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<td>DYT10 (16p11.2-q12.1, causing paroxysmal kinesigenic choreoathetosis [PKC])</td>
<td>Methylmalonic aciduria</td>
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<td>DYT11 (heterogeneous, causing familial myoclonus-dystonia)</td>
<td>Tyrosinemia</td>
<td>Wasp sting</td>
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<td>Rapid-onset dystonia-parkinsonism (DYT12)</td>
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<tr>
<td>Fahr disease (often caused by hypoparathyroid disease)</td>
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<tr>
<td>Pantothenate kinase-associated neurodegeneration (PKAN; neuronal brain iron accumulation type 1, formerly Hallervorden-Spatz disease, caused by mutations in PANK2)</td>
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<td>Huntington disease (particularly the Westphal variant, IT15-4p16.3)</td>
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<td>Spincerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)</td>
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<td>Neuronal ceroid-lipofuscinoses (NCL)</td>
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<td>Rett syndrome</td>
<td>Ataxia-telangiectasia</td>
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<td>Striatal necrosis</td>
<td>Tay-Sachs disease</td>
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<td>Leigh disease</td>
<td>Sandhoff's disease</td>
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<td>Neuroacanthocytosis</td>
<td>Niemann-Pick type C</td>
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<tr>
<td>HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)</td>
<td>GM, gangliosidosis</td>
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<td>Ataxia-telangiectasia</td>
<td>Metachromatic leukodystrophy (MLD)</td>
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<td>Lesch-Nyhan disease</td>
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</table>
### Paroxysmal Disorders

- Paroxysmal kinesigenic choreoathetosis (PKC)
- Paroxysmal nonkinesigenic choreoathetosis (PNKC)
- Exercise-induced dystonia
- Complex migraine
- Alternating hemiplegia of childhood (AHC)
- Paroxysmal torticollis of infancy

### Disorders That Mimic Dystonia

- Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)
- Arnold-Chiari malformation type II
- Atlantoaxial subluxation
- Syringomyelia
- Posterior fossa mass
- Cervical spine malformation (including Klippel-Feil syndrome)
- Skew deviation with vertical diplopia causing neck twisting
- Juvenile rheumatoid arthritis
- Sandifer syndrome (associated with hiatal hernia in infants)
- Spasms nutans
- Tics
- Infant masturbation
- Spasticity
- Myotonia
- Rigidity
- Stiff-person syndrome
- Isaacs syndrome (neuromyotonia)
- Starle disease (hyperekplexia)
- Neuroleptic malignant syndrome
- Central herniation with posturing
- Psychogenic dystonia

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### Table 597-11 | Examples of Primary and Secondary Dystonia in Childhood

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<th>ADDITIONAL CLINICAL FEATURES</th>
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<td>Sterile pyrexias</td>
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<td>Lesions on the digits, ears (chilblain)</td>
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<td>CT: calcification of the basal ganglia</td>
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<td>Alternating hemiplegia of childhood</td>
<td>Episodic hemiplegia/quadriplegia</td>
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<td>Abnormal ocular movements</td>
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<td>Autonomic symptoms</td>
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<td>Epilepsy</td>
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<td>Global developmental impairment</td>
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<td>Environmental triggers for spells</td>
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<td>Aromatic amino acid decarboxylase deficiency (AADC)</td>
<td>Developmental delay</td>
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<td>Oculogyric crises</td>
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<td>ARX gene mutation (X-linked)</td>
<td>Male</td>
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<td>Cognitive impairment</td>
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<td>Infantile spasms, epilepsy</td>
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<td>Brain malformation</td>
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<td>Benign paroxysmal torticollis of infancy</td>
<td>Episodic</td>
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<td>Cervical dystonia only</td>
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<td>Family history of migraine</td>
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<td>Complex regional pain syndrome</td>
<td>Lower limb involvement</td>
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<td>Prominent pain</td>
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<td>Dopa-responsive dystonia (DRD)</td>
<td>Diurnal variation</td>
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<td>Drug-induced dystonia</td>
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<td>Dystonia-deafness optic neuropathy syndrome</td>
<td>Sensorineural hearing loss in early childhood</td>
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<td>Psychosis</td>
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<td>Optic atrophy in adolescence</td>
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<td>DYT1 dystonia</td>
<td>Lower limb onset followed by generalization</td>
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<td>Glutaric aciduria type 1</td>
<td>Macrocephaly</td>
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<td></td>
<td>Encephalopathic crises</td>
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<td>MRI: striatal necrosis</td>
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<td>GM1 gangliosidosis type 3</td>
<td>Short stature, skeletal dysplasia</td>
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<td>Orofacial dystonia</td>
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<td>Speech/swallowing disturbance</td>
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<td>Parkininson</td>
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<td>MRI: putaminal hyperintensity</td>
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<td>Huntington disease</td>
<td>Parkininson</td>
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<td>Epilepsy</td>
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<td></td>
<td>Family history of Huntington disease</td>
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<tr>
<td>Kernicterus</td>
<td>Jaundice in infancy</td>
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<td>Hearing loss</td>
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<td>Impaired upgaze</td>
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<td>Enamel dysplasia</td>
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<td>MRI: hyperintense lesions in the globus pallidus</td>
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<tr>
<td>Neuroacanthocytosis</td>
<td>Oromandibular and lingual dystonia</td>
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<tr>
<td>Neurodegeneration with brain iron accumulation</td>
<td>Cognitive impairment</td>
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<td></td>
<td>Retinal pigmentary degeneration, optic atrophy</td>
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<tr>
<td>Rapid onset dystonia parkinsonism (DYT12)</td>
<td>Acute onset</td>
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<tr>
<td></td>
<td>Distribution face &gt; arm &gt; leg</td>
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<td></td>
<td>Prominent bulbar signs</td>
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<tr>
<td>Rett syndrome</td>
<td>Female</td>
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<tr>
<td></td>
<td>Developmental regression following a period of normal development</td>
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<td></td>
<td>Stereotypic hand movements</td>
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<td></td>
<td>Acquired microcephaly</td>
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<td></td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 17 (SCA17)</td>
<td>Ataxia</td>
</tr>
<tr>
<td></td>
<td>Dementia, psychiatric symptoms</td>
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<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td>Stereotyped movements</td>
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<td></td>
<td>Premonitory urge, suppressible</td>
</tr>
<tr>
<td>Tics</td>
<td>Stereotyped movements</td>
</tr>
<tr>
<td></td>
<td>Premonitory urge, suppressible</td>
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</tbody>
</table>

Triphosphate (ATP) binding protein torsinA. The initial manifestation of DYT1 dystonia is often intermittent unilateral posturing of a lower extremity, which assumes an extended and rotated position. Ultimately, all 4 extremities and the axial musculature can be affected, but the dystonia may also remain localized to one limb. Cranial involvement can occur in DYT1 dystonia, but it is uncommon compared to non-DYT1 dystonias. There is a wide clinical spectrum, varying even within families. If a family history of dystonia is absent, the diagnosis should still be considered, given the intrafamilial variability in clinical expression.

More than a dozen loci for genes for torsion dystonia have been identified (DYT1-DYT24). One is the autosomal dominant disorder dopa-responsive dystonia (DRD, DYT5a), also called Segawa syndrome. The gene for DRD codes for guanosine triphosphate cyclohydrolase 1, the rate-limiting enzyme for tetrahydrobiopterin synthesis, which is a cofactor for synthesis of the neurotransmitters dopamine.
and serotonin. Thus, the genetic mutation results in dopamine deficiency. The hallmark of the disorder, particularly in adolescents and adults, is diurnal variation: symptoms worsen as the day progresses and may transiently improve with sleep. Early-onset patients, who tend to present with delayed or abnormal gait from dystonia of a lower extremity, can easily be confused with patients with dystonic cerebral palsy. It should be noted that in the presence of a progressive dystonia, diurnal fluctuation, or if loss of previously achieved motor skills occurs, a prior diagnosis of cerebral palsy should be reexamined. DRD responds dramatically to small daily doses of levodopa. The responsiveness to levodopa is a sustained benefit, even if the diagnosis is delayed several years, as long as contractures have not developed.

**Myoclonus dystonia (DYTT11)**, caused by mutations in the epsilon-sarcoglycan (SCGE) gene, is characterized by dystonia involving the upper extremities, head, and/or neck, as well as myoclonic movements in these regions. Although a combination of myoclonus and dystonia typically occurs, each manifestation can present in isolation. When repetitive, the myoclonus may take on a tremor-like appearance, termed dystonic tremor. Improvement in symptoms following alcohol ingestion, reported by affected adult family members, may be a helpful clue to this diagnosis.

Common to the inherited dystonias, there is considerable intrafamilial variability in clinical manifestations, distribution, and severity of dystonia. In primary dystonias, although the main clinical features are motor, there may be an increased risk for major depression. Anxiety, obsessive-compulsive disorder, and depression have all been reported in the myoclonus–dystonia syndrome. Screening for psychiatric comorbidities cannot be overlooked in this population.

**DRUG-INDUCED DYSTONIAS**

A number of medications are capable of inducing involuntary movements, drug-induced movement disorders, in children and adults. Dopamine-blocking agents, including antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine), as well as atypical antipsychotics (e.g., risperidone) can produce acute dystonic reactions or delayed (tardive) drug-induced movement disorders. **Acute dystonic reactions**, occurring in the 1st days of exposure, typically involve the face and neck, manifesting as torticollis, retrocollis, oculogyric crisis, or tongue protrusion. Life-threatening presentations with laryngospasm and airway compromise can also occur, requiring prompt recognition and treatment of this entity. Intravenous diphenhydramine, 1-2 mg/kg/dose, may rapidly reverse the drug-related dystonia. The high potency of the dopamine blocker, young age, and prior dystonic reactions may be predisposing factors. Acute dystonic reactions have also been described with cetirizine.

Severe rigidity combined with high fever, autonomic symptoms (tachycardia, diaphoresis), delirium, and dystonia are signs of neuroleptic malignant syndrome, which typically occurs a few days after starting or increasing the dose of a neuroleptic drug, or in the setting of withdrawal from a dopaminergic agent. In contrast to acute dystonic reactions, which take place within days, neuroleptic malignant syndrome occurs within a month of medication initiation or dose increase.

Delayed onset involuntary movements, **tardive dyskinesias**, develop in the setting of chronic (>3 mo duration) neuroleptic use. Involvement of the face, particularly the mouth, lips, and/or jaw with chewing or tongue thrusting is characteristic. The risk of tardive dyskinesia, which is much less frequent in children compared to adults, increases as medication dose and duration of treatment increase. There are data to suggest that children with autism spectrum disorders may also be at increased risk for this drug-induced movement disorders. Unlike acute dystonic reactions and neuroleptic malignant syndrome, discontinuation of the offending agent may not result in clinical improvement. In these patients, use of dopamine-depleters, such as reserpine or tetrabenazine, may prove helpful.

Therapeutic doses of phenytoin or carbamazepine rarely cause progressive dystonia in children with epilepsy, particularly in those who have an underlying structural abnormality of the brain.

During evaluation of new onset dystonia, a careful history of prescriptions and potential medication exposures is critical.

**CEREBRAL PALSY**

See Chapter 598.

**METABOLIC DISORDERS**

Disorders of monamine neurotransmitter metabolism, of which DRD is one, present in infancy and early childhood with dystonia, hypotonia, oculogyric crises, and/or autonomic symptoms. The more common disorders among this group of rare diseases include DRD, tyrosine hydroxylase deficiency, and aromatic amino acid decarboxylase deficiency. Abnormalities of the dopamine transporter (DAT) can also present in infancy with dystonia. Detailed discussion is beyond the scope of this chapter; reviews, however, are available for reference.

**Wilson disease** is an autosomal recessive inborn error of copper transport characterized by cirrhosis of the liver and degenerative changes in the central nervous system, particularly the basal ganglia (see Chapter 357.2). It has been determined that there are multiple mutations in the Wilson disease gene (WND), accounting for the variability in presentation of the condition. The neurologic manifestations of Wilson disease rarely appear before age 10 yr, and the initial sign is often progressive dystonia. Tremors of the extremities develop, unilaterally at first, but they eventually become coarse, generalized, and incapacitating. Other neurologic signs of Wilson disease relate to progressive basal ganglia disease, such as parkinsonism, dysarthria, dysphonia, and choreoathetosis. Less frequent are ataxia and pyramidal signs. The MRI or CT scan shows ventricular dilation in advanced cases with atrophy of the cerebrum, cerebellum, and/or brainstem, along with signal intensity change in the basal ganglia, thalamus, and/or brainstem, particularly the midbrain.

Pantothenate kinase–associated neurodegeneration (formerly known as Hallervorden-Spatz disease) is a rare autosomal recessive neurodegenerative disorder. Many patients have mutations in pantothenate kinase 2 (PANK2) localized to mitochondria in neurons. The condition usually begins before 6 yr of age and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity (tissue necrosis and edema), or “eye-of-the-tiger” sign (Fig. 597-1). Neuropathologic examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. More recently, similar disorders of high brain iron content without PANK2 mutations, including infantile neuroaxonal dystrophy, neuroferritinopathy, and aceruloplasminemia, have been grouped as disorders of neurodegeneration with brain iron accumulation. Patterns of iron deposition visualized by brain MRI have shown utility in differentiating these disorders.

**Biotin-responsive basal ganglia disease** manifests with episodes of acute dystonia, external ophthalmoplegia and encephalopathy. SLC19A3 is the responsible mutated gene. MRI demonstrates involvement of the basal ganglia, with vasogenic edema and the “bat-wing” sign (Fig. 597-2). Treatment with biotin and thiamine results in improvement in 2-4 days.

Although dystonia may present in isolation as the first sign of a metabolic or neurodegenerative disorder, this group of diseases should be considered mainly in those who demonstrate signs of systemic disease, (e.g., organomegaly, short stature, hearing loss, vision impairment, epilepsy), those with episodes of severe illness, evidence of regression, or cognitive impairment. Table 597-11 outlines additional features suggestive of specific disorders.

**OTHER DISORDERS**

Although uncommon, movement disorders, including dystonia, may be part of the presenting symptoms of complex regional pain syndrome. Onset of involuntary movements within 1 yr of the traumatic event, affected lower limb, pain disproportionate to inciting event, and changes in the overlying skin and blood flow to the affected area suggest complex regional pain syndrome. Although sustained dystonia...
patients are also affected by episodes of dystonia, ranging from minutes to days in duration. On average, both features of the disorder commence at approximately 6 mo of age. Episodic abnormal eye movements are observed in a large proportion of patients (93%) with onset as early as the 1st wk of life. Alternating hemiplegia of childhood is associated with mutations in the \textit{ATP1A2} and \textit{ATP1A3} genes. Alternating hemiplegia of childhood can similarly be triggered by fluctuations in temperature, certain foods, or water exposure. Over time, epilepsy and cognitive impairment emerge, and the involuntary movements change from episodic to constant. Infantile onset and the paroxysmal nature of symptoms early in the disease course are key features to this diagnosis.

Finally, although a diagnosis of exclusion, the presence of odd movements or selective disability may indicate a psychogenic dystonia in older children. There is considerable overlap in features of organic and can produce pain or discomfort, complex regional pain syndrome should be considered in those who have a prominent component of pain and recent history of trauma to the affected limb.

There are disorders unique to childhood that warrant exploration in this section. Benign paroxysmal torticollis of infancy is characterized by recurrent episodes of cervical dystonia beginning in the 1st few mo of life. The torticollis may alternate sides from 1 episode to the next and may also persist during sleep. Associated signs and symptoms include irritability, pallor, vomiting, vertigo, ataxia, and occasionally limb dystonia. Family history is often notable for migraine and/or motion sickness in 1st-degree relatives. Despite the high frequency of spells, imaging studies are normal, and the outcome is uniformly benign with resolution by 3 yr of age.

In alternating hemiplegia of childhood, episodic hemiplegia affecting either side of the body is the hallmark of the disorder. However,
psychogenic movement disorders, making the diagnosis difficult to establish. For instance, both organic and psychogenic movement disorders have the potential to worsen in the setting of stress and may dissipate with relaxation or sleep. History should include review of recent stressors, psychiatric symptoms, and exposure to others with similar disorders. On examination, a changing movement disorder, inconsistent motor or sensory exam, or response to suggestion, are supportive of a possible psychogenic movement disorder. Early recognition of this disorder may lessen morbidity caused by unnecessary diagnostic and interventional procedures.

**TREATMENT**

Children with generalized dystonia, including those with involvement of the muscles of swallowing, may respond to the anticholinergic agent trihexyphenidyl (Artane). Titration occurs slowly over the course of months in an effort to limit untoward side effects, such as urinary retention, mental confusion, or blurred vision. Additional drugs that have been effective include levodopa and diazepam. Segmental dystonia, such as torticollis, often responds well to botulinum toxin injections. Intrathecal baclofen delivered through implantable constant infusion pump may be helpful in some patients. Deep brain stimulation with leads implanted in the globus pallidus is most helpful for children with severe primary generalized dystonia. Recent data suggest, however, that deep brain stimulation may also be of benefit in children with secondary dystonias, such as cerebral palsy.

In the case of drug-induced dystonias, removal of the offending agent and treatment with intravenous diphenhydramine typically suffices. For neuroleptic malignant syndrome, dantrolene may be indicated.

*Bibliography is available at Expert Consult.*
Cerebral palsy (CP) is a diagnostic term used to describe a group of permanent disorders of movement and posture causing activity limitation, that are attributable to nonprogressive disturbances in the developing fetal or infant brain. The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as by epilepsy and secondary musculoskeletal problems. CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other acquired etiologies that produce a common group of neurologic phenotypes. CP has historically been considered a static encephalopathy, but some of the neurologic features of CP, such as movement disorders and orthopedic complications, including scoliosis and hip dislocation, can change or progress over time. Many children and adults with CP function at a high educational and vocational level, without any sign of cognitive dysfunction.

Epidemiology and Etiology

CP is the most common and costly form of chronic motor disability that begins in childhood; data from the Centers for Disease Control and Prevention indicate that the incidence is 3.6 per 1,000 children with a male:female ratio of 1.4:1. The Collaborative Perinatal Project, in which approximately 45,000 children were regularly monitored from in utero to the age of 7 yr, found that most children with CP had been born at term with uncomplicated labors and deliveries. In 80% of cases, features were identified pointing to antenatal factors causing abnormal brain development. A substantial number of children with CP had congenital anomalies external to the central nervous system (CNS). Fewer than 10% of children with CP had evidence of intrapartum asphyxia. Intrauterine exposure to maternal infection (chorioamnionitis, inflammation of placental membranes, umbilical cord inflammation, foul-smelling amniotic fluid, maternal sepsis, temperature >38°C [100.4°F] during labor, urinary tract infection) was associated with a significant increase in the risk of CP in normal birthweight infants. Elevated levels of inflammatory cytokines have been reported in heelstick blood collected at birth from children who later were identified with CP. Genetic factors may contribute to the inflammatory cytokine response, and a functional polymorphism in the interleukin-6 gene is associated with a higher rate of CP in term infants.

The prevalence of CP has increased somewhat as a result of the enhanced survival of very premature infants weighing <1,000 g, who go on to develop CP at a rate of approximately 15 per 100. However, the gestational age at birth-adjusted prevalence of CP among 2 yr old former premature infants born at 20-27 wk of gestation has decreased over the past decade. The major lesions that contribute to CP in preterm infants are intracerebral hemorrhage and periventricular leukomalacia (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 wk of gestational age among former preterm infants are a predictor of later CP.

In 2006, the European Cerebral Palsy Study examined prenatal and perinatal factors as well as clinical findings and results of MRI in a contemporary cohort of more than 400 children with CP. In agreement with the Collaborative Perinatal Project study, more than half the children with CP in this study were born at term, and less than 20% had clinical or brain imaging indicators of possible intrapartum factors such as asphyxia. The contribution of intrapartum factors to CP is higher in some underdeveloped regions of the world. Also in agreement with earlier data, antenatal infection was strongly associated with CP and 39.5% of mothers of children with CP reported having an infection during the pregnancy, with 19% having evidence of a urinary tract infection and 11.5% reporting taking antibiotics. Multiple pregnancy was also associated with a higher incidence of CP and 12% of the cases in the European CP study resulted from a multiple pregnancy, in contrast to a 1.5% incidence of multiple pregnancy in the study. Other studies have also documented a relationship between multiple births and CP, with a rate in twins that is 5-8 times greater than in singleton pregnancies and a rate in triplets that is 20-47 times greater. Death of a twin in utero carries an even greater risk of CP that is 8 times that of a pregnancy in which both twins survive and approximately 60 times the risk in a singleton pregnancy. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. Among children from multiple pregnancies, 24% were from pregnancies after infertility treatment compared with 3.4% of the singleton pregnancies in the study. CP is more common and more severe in boys compared to girls and this effect is enhanced at the extremes of body weight. Male infants with intrauterine growth retardation and a birthweight less than the 3rd percentile are 16 times more likely to have CP than males with optimal growth, and infants with weights above the 97th percentile are 4 times more likely to have CP.
Encephalopathies
Classification of Cerebral Palsy and Major Causes

**CLINICAL MANIFESTATIONS**

CP is generally divided into several major motor syndromes that differ according to the pattern of neurologic involvement, neuropathology, and etiology (Table 598-1). The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities. CP is also commonly associated with a spectrum of developmental disabilities, including intellectual impairment, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities. The motor handicap may be the least of the child’s problems.

Infants with spastic hemiplegia have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 yr of age. Walking is usually delayed until 18-24 mo, and a circumscribed gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremit growth is influenced by this area of the brain. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe because of the increased tone in the antigravity gastrocnemius muscles, and the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. About one-third of patients with spastic hemiplegia have a seizure disorder that usually develops in the 1st yr or 2; approximately 25% have cognitive abnormalities including mental retardation. MRI is far more sensitive than CT for most lesions seen with CP, although a CT scan may be useful for detecting calcifications associated with congenital infections. In the European CP study, 34% of children with hemiplegia had injury to the white matter that probably dated to the in utero period and 27% had a focal lesion that may have resulted from a stroke. Other children with hemiplegic CP had had malformations from multiple causes including infections (e.g., cytomegalovirus), lissencephaly, polymicrogyria, schizencephaly, or cortical dysplasia. Focal cerebral infarction (stroke) secondary to intrauterine or perinatal thromboembolism related to thrombophilic disorders, like the presence of anticardiolipin antibodies, is an important cause of hemiplegic CP (see Chapter 601). Family histories suggestive of thrombosis and inherited clotting disorders, such as factor V Leiden mutation, may be present and evaluation of the mother may provide information valuable for future pregnancies and other family members.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with damage to the immature white matter during the vulnerable period of immature oligodendroglia between 20-34 wk of gestation. However, approximately 15% of cases of spastic diplegia result from in utero lesions in infants who go on to delivery at term. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal 4-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. If there is paraspinal muscle involvement, the child may be unable to sit. Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoe. Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development for these patients is good, and the likelihood of seizures is minimal. Such children often have learning disabilities and deficits in other abilities, such as vision, because of disruption of multiple white matter pathways that carry sensory as well as motor information.

The most common neuropathologic finding in children with spastic diplegia is PVL, which is visualized on MRI in more than 70% of cases. MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles. However, neuropathology has also demonstrated a reduction in oligodendroglia in more widespread subcortical regions beyond the periventricular zones, and these subcortical lesions may contribute to the learning problems these patients can have. MRI with diffusion tensor imaging is being used to map white matter tracks more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 598-1). These observations have led to greater interest in the importance of sensory deficits in these patients, which may be important for designing rehabilitative techniques.

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with intellectual disability and seizures. Swallowing difficulties are common as a result of supranuclear bulbar palsy, often leading to aspiration pneumonia. The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees and elbows are often present by late childhood. Associated

<table>
<thead>
<tr>
<th>MOTOR SYNDROME (APPROX. % OF CP)</th>
<th>NEUROPATHOLOGY/MRI</th>
<th>MAJOR CAUSES</th>
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<td>Spastic diplegia (35%)</td>
<td>Periventricular leukomalacia</td>
<td>Prematurity</td>
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<td>Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles</td>
<td>Ischemia</td>
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<td>Infection</td>
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<td></td>
<td>Endocrine/metabolic (e.g., thyroid)</td>
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<td>Spastic quadriplegia (20%)</td>
<td>Periventricular leukomalacia</td>
<td>Ischemia, infection</td>
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<td>Multicystic encephalomalacia</td>
<td>Endocrine/metabolic, genetic/developmental</td>
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<td>Cortical malformations</td>
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<tr>
<td>Hemiplegia (25%)</td>
<td>Stroke: in utero or neonatal</td>
<td>Thrombophilic disorders</td>
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<td>Focal infarct or cortical, subcortical damage</td>
<td>Genetic/developmental</td>
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<tr>
<td></td>
<td>Cortical malformations</td>
<td>Periventricular hemorrhagic infarction</td>
</tr>
<tr>
<td>Extrapyramidal (athetoid, dysskinetic) (15%)</td>
<td>Asphyxia: symmetric scars in putamen and thalamus</td>
<td>Asphyxia</td>
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<td>Kernicterus: scars in globus pallidus, hippocampus</td>
<td>Kernicterus</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial: scarring globus pallidus, caudate, putamen, brainstem</td>
<td>Mitochondrial</td>
</tr>
<tr>
<td></td>
<td>No lesions: ? dopa-responsive dystonia</td>
<td>Genetic/metabolic</td>
</tr>
</tbody>
</table>

Kernicterus: scars in globus pallidus, hippocampus
Cortical malformations
Focal infarct or cortical, subcortical damage
Cortical malformations
Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles
Periventricular leukomalacia
Asphyxia: symmetric scars in putamen and thalamus
Kernicterus: scars in globus pallidus, hippocampus
Mitochondrial: scarring globus pallidus, caudate, putamen, brainstem
Prematurity
Ischemia
Infection
Endocrine/metabolic
Ischemia, infection
Endocrine/metabolic, genetic/developmental
Thrombophilic disorders
Infection
Genetic/developmental
Periventricular hemorrhagic infarction
Asphyxia
Kernicterus
Mitochondrial
Genetic/metabolic

Table 598-1 Classification of Cerebral Palsy and Major Causes
Lesions in the basal ganglia and thalamus caused by metabolic genetic disorders such as mitochondrial disorders and glutaric aciduria. MRI scanning and possibly metabolic testing are important in the evaluation of children with extrapyramidal CP to make a correct etiologic diagnosis. In patients with dystonia who have a normal MRI, it is important to have a high level of suspicion for dihydroxyphenylalanine (DOPA)-responsive dystonia (Segawa disease), which causes prominent dystonia that can resemble CP. These patients typically have diurnal variation in their signs with worsening dystonia in the legs during the day; however, this may not be prominent. These patients can be tested for a response to small doses of L-dopa and/or cerebrospinal fluid can be sent for neurotransmitter analysis.

Associated comorbidities are common and include pain (in 75%), cognitive disability (50%), hip displacement (30%), seizures (25%), behavioral disorders (25%), sleep disturbances (20%), visual impairment (19%), and hearing impairment (4%).

DIAGNOSIS

A thorough history and physical examination should preclude a progressive disorder of the CNS, including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy. The possibility of anomalies at the base of the skull or other disorders affecting the cervical spinal cord needs to be considered in patients with little involvement of the arms or cranial nerves. An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations; an MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. Additional studies may include tests of hearing and visual function. Genetic evaluation should be considered in patients with congenital malformations (chromosomes) or evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy). In addition to the genetic disorders mentioned earlier that can present as CP,
the urea cycle disorder arginase deficiency is a rare cause of spastic diplegia and a deficiency of sulfite oxidase or molybdenum cofactor can present as CP caused by perinatal asphyxia. Tests to detect inherited thrombophilic disorders may be indicated in patients in whom an in utero or neonatal stroke is suspected as the cause of CP.

Because CP is usually associated with a wide spectrum of developmental disorders, a multidisciplinary approach is most helpful in the assessment and treatment of such children.

**TREATMENT**

Some progress has been made in both prevention of CP before it occurs and treatment of children with the disorder. Preliminary results from controlled trials of magnesium sulfate given intravenously to mothers in premature labor with birth imminent before 32 wk gestation showed significant reduction in the risk of CP at 2 yr of age. Nonetheless, one study that followed preterm infants whose mothers received magnesium sulfate demonstrated no benefit in terms of the incidence of CP and abnormal motor, cognitive, or behavioral function at school age. Furthermore, several large trials have shown that cooling term infants with hypoxic–ischemic encephalopathy to 33.5°C (91.9°F) for 3 days, starting within 6 hr of birth, reduces the risk of dyskinetic or spastic quadriplegia form of CP.

For children who have a diagnosis of CP, a team of physicians, including neurodevelopmental pediatricians, pediatric neurologists, and physical medicine and rehabilitation specialists, as well as occupational and physical therapists, speech pathologists, social workers, educators, and developmental psychologists, is important to reduce abnormalities of movement and tone and to optimize normal psychomotor development. Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that limit the effects of abnormal muscle tone. They also need to be instructed in the supervision of a series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon. Physical and occupational therapies are useful for promoting mobility and the use of the upper extremities for activities of daily living. Speech language pathologists promote acquisition of a functional means of communications. These therapists help children to achieve their potential and often recommend further evaluations and adaptive equipment.

Children with spastic diplegia are treated initially with the assistance of adaptive equipment, such as walkers, poles, and standing frames. If a patient has marked spasticity of the lower extremities or evidence of hip dislocation, consideration should be given to performing surgical soft-tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release. A rhizotomy procedure in which the roots of the spinal nerves are divided produces considerable improvement in selected patients with severe spastic diplegia (Fig. 598-2). A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon. Quadriplegia is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrange-
ments. The function of the affected extremities in children with hemiplegic CP can often be improved by therapy in which movement of the good side is constrained with casts while the impaired extremities perform exercises which induce improved hand and arm functioning. This constraint-induced movement therapy is effective in patients of all ages.

Several drugs have been used to treat spasticity, including benzodiazepines and baclofen. These medications have beneficial effects in some patients but can also cause side effects such as sedation for benzodiazepines and lowered seizure threshold for baclofen. Several drugs can be used to treat spasticity, including oral diazepam (0.01–0.3 mg/kg/day, divided bid or qid), baclofen (0.2–2 mg/kg/day, divided bid or tid) or dantrolene (0.5–10 mg/kg/day, bid). Small doses of levodopa (0.5–2 mg/kg/day) can be used to treat dystonia or DOPA-responsive dystonia. Artane (trihexyphenidyl, 0.25 mg/day, divided bid or tid and titrated upward) is sometimes useful for treating dystonia and can increase use of the upper extremities and vocalizations.

Intrathecal baclofen delivered with an implanted pump has been used successfully in many children with severe spasticity, and can be useful because it delivers the drug directly around the spinal cord where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood–brain barrier. This therapy requires a team approach and constant follow-up for complications of the infusion pumping mechanism and infection. Botulinum toxin injected into specific muscle groups for the management of spasticity shows a very positive response in many patients. Botulinum toxin injected into salivary glands may also help reduce the severity of drooling, which is seen in 10–30% of patients with CP and has been traditionally treated with anticholinergic agents. Patients with rigidity, dystonia, and spastic quadriparesis sometimes respond to levodopa, and children with dystonia may benefit from carbamazepine or trihexyphenidyl. Hyperbaric oxygen has not been shown to improve the condition of children with CP.

Communication skills may be enhanced by the use of Bliss symbols, talking typewriters, electronic speech generating devices, and specially adapted computers including artificial intelligence computers to augment motor and language function. Significant behavior problems may substantially interfere with the development of a child with CP; their early identification and management are important, and the assistance of a psychologist or psychiatrist may be necessary. Learning and attention deficit disorders and mental retardation are assessed and managed by a psychologist and educator. Strabismus, nystagmus, and optic atrophy are common in children with CP; an ophthalmologist should be included in the initial assessment. Lower urinary tract dysfunction should receive prompt assessment and treatment.

*Bibliography is available at Expert Consult.*

Figure 598-2 Schematic of the technique of selected dorsal rhizotomy. A, After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. B, A proportion of rootlets are transected. (From Koman LA, Smith BP, Shilt JS: Cerebral palsy, Lancet 363:1619–1631, 2004. Reproduced with permission from Wake Forest University Orthopaedic Press.)
Bibliography


Mitochondrial encephalomyopathies are a heterogeneous group of clinical syndromes caused by genetic lesions that impair energy production through oxidative phosphorylation. The signs and symptoms of these disorders reflect the vulnerability of the nervous system, muscles, and other organs to energy deficiency. Signs of brain and muscle dysfunction (seizures, weakness, ptosis, external ophthalmoplegia, psychomotor regression, hearing loss, movement disorders, and ataxia) in association with lactic acidosis are prominent features of mitochondrial disorders. Cardiomyopathy and diabetes mellitus can also result from mitochondrial disorders.

Children with mitochondrial disorders often have multifocal signs that are intermittent or relapsing–remitting, often in association with intercurrent illness. Many of these disorders were described as clinical syndromes before their genetics were understood. Children with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) present with developmental delay, weakness, and headaches, as well as focal signs that suggest a stroke. Brain imaging indicates that injury does not fit within the usual vascular territories. Children with myoclonic epilepsy with ragged red fibers (MERRF) present with myoclonus and myoclonic seizures as well as intermittent muscle weakness. The ragged red fibers referred to in the name of this disorder are clumps of abnormal mitochondria seen within muscle fibers in sections from a muscle biopsy stained with Gomori trichrome stain. NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa), Kearns-Sayre syndrome (KSS; ptosis, ophthalmoplegia, heart block), Leigh disease (subacute necrotizing encephalomyelopathy), and Leber hereditary optic neuropathy (LHON) are also defined as relatively homogeneous clinical subgroups (Table 598-2). It is important to keep in mind that mitochondrial disorders can be difficult to diagnose. They often present with novel combinations of signs and symptoms as a consequence of high mutation rates for mitochondrial DNA (mtDNA), and the severity of disease varies from person to person.

Mitochondrial diseases can be caused by mutations of nuclear DNA (nDNA) or mtDNA (see Chapters 80, 86, and 87). Oxidative phosphorylation in the respiratory chain is mediated by 4 intramitochondrial enzyme complexes (complexes I-IV) and 2 mobile electron carriers (coenzyme Q and cytochrome c) that create an electrochemical proton gradient utilized by complex V (adenosine triphosphate [ATP] synthase) to create the ATP required for normal cellular function. The maintenance of oxidative phosphorylation requires coordinated regulation of nuclear DNA and mtDNA genes. Human mtDNA is a small (16.6 kb), circular, double-stranded molecule that has been completely sequenced and encodes 37 genes including 13 structural proteins, all of which are subunits of the respiratory chain complexes, as well as 2 ribosomal RNAs and 22 transfer RNAs (tRNAs) needed for translation. The nuclear DNA is responsible for synthesizing approximately 70 subunits, transporting them to the mitochondria via chaperone proteins, ensuring their passage across the inner mitochondrial membrane, and coordinating their correct processing and assembly. Diseases of mitochondrial oxidative phosphorylation can be divided into 3 groups: (1) defects of mtDNA, (2) defects of nDNA, and (3) defects of communication between the nuclear and mitochondrial genome. mtDNA is distinct from nDNA for the following 4 reasons: (1) its genetic code differs from nDNA, (2) it is tightly packed with information because it contains no introns, (3) it is subject to spontaneous mutations at a higher rate than nDNA, (4) it has less efficient repair mechanisms.

Inheritance of mutations present on mtDNA is nonmendelian and can be complex. At fertilization, mtDNA is present in hundreds or thousands of copies per cell and is transmitted by maternal inheritance from her oocyte to all her children, but only her daughters can pass it on to their children. Through the process called heteroplasmy or threshold effect, mtDNA containing mutations can be distributed unequally between cells in specific tissues. Some cells receive few or no mutant genomes (normal or wild-type homoplasy), whereas

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<th>MERRF</th>
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KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia and retinitis pigmentosa; RRF, ragged red fibers.
others receive a mixed population of mutant and wild-type mtDNAs (heteroplasmay), and still others receive primarily or exclusively mutant genomes (mutant homoplasy). The important implications of maternal inheritance and heteroplasmay are as follows: (1) inheritance of the disease is maternal, but both sexes are equally affected; (2) phenotypic expression of an mtDNA mutation depends on the relative proportions of mutant and wild-type genomes, with a minimum critical number of mutant genomes required for expression (threshold effect); (3) at cell division, the proportional distribution may shift between daughter cells (mitotic segregation), leading to a corresponding phenotypic change; and (4) subsequent generations are affected at a higher rate than in autosomal dominant diseases. The critical number of mutant mtDNAs required for the threshold effect may vary, depending on the vulnerability of the tissue to impairments of oxidative metabolism as well as on the vulnerability of the same tissue over time that may increase with aging. In contrast to maternal inherited disorders caused by mutations in mtDNA, diseases resulting from defects in nDNA follow mendelian inheritance. Mitochondrial diseases caused by defects in nDNA include defects in substrate transport (plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase defects), defects in substrate oxidation (pyruvate dehydrogenase complex, pyruvate carboxylase, intramitochondrial fatty acid oxidation defects), defects in the Krebs cycle (α-ketoglutarate dehydrogenase, fumarase, aconitate defects), and defects in the respiratory chain (complexes I-V), including defects of oxidation/phosphorylation coupling (Luft syndrome), and defects in mitochondrial protein transport.

Diseases caused by defects in mtDNA can be divided into those associated with point mutations that are maternally inherited (e.g., LHON, MELAS, MERRF, and NARP syndromes) and those caused by deletions or duplications of mtDNA that reflect altered communication between the nucleus and the mitochondria (KSS; Pearson syndrome, a rare severe encephalopathy with anemia and pancreatic dysfunction; and progressive external ophthalmoplegia). These disorders can be inherited by sporadic, autosomal dominant or recessive mechanisms and mutations in multiple genes, including mitochondrial mtDNA polymerase γ catalytic subunit (POLG), have been identified. POLG mutations have also been identified in patients with Alpers-Huttenlocher syndrome, which causes a refractory seizure disorder and hepatic failure as well as autosomal dominant and recessive progressive external ophthalmoplegia, childhood myocerebrohepatopathy spectrum disorders, myoclonic epilepsy myopathy sensory ataxia syndrome, and POLG-related ataxia neuropathy spectrum disorders. Other genes that regulate the supply of nucleotides for mtDNA synthesis are associated with severe encephalopathy and liver disease, and new disorders are being identified that result from defects in the interactions between mitochondria and their milieu in the cell.

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKELIKE EPISODES

Children with MELAS may be normal for the 1st several yr, but they gradually display delayed motor and cognitive development and short stature. The clinical syndrome is characterized by (1) recurrent stroke-like episodes of hemiparesis or other focal neurologic signs with lesions most commonly seen in the posterior temporal, parietal, and occipital lobes (CT or MRI evidence of focal brain abnormalities); (2) lactic acidosis, ragged red fibers (RRF), or both; and (3) at least 2 of the following: focal or generalized seizures, dementia, recurrent migraine headaches, and vomiting. In 1 series, onset was before age 15 yr in 62% of patients, and hemianopia or cortical blindness was the most common manifestation. Cerebrospinal fluid protein is often increased. The MELAS 3243 mutation on mtDNA is the most common mutation to produce MELAS and can also be associated with different combinations of exercise intolerance, myopathy, ophthalmoplegia, pigmentary retinopathy, hypertrophic or dilated cardiomyopathy, cardiac conduction defects, deafness, endocrinopathy (diabetes mellitus), and proximal renal tubular dysfunction. A number of other mutations have been reported, and 2 patients have been described with bilateral rolandic lesions and epilepsy partialis continua associated with mtDNA mutations at 10158>T>C and 10191>T>C. MELAS is a progressive disorder that has been reported in siblings. However, most maternal relatives of MELAS patients are mildly affected or unaffected. MELAS is punctuated with episodes of stroke leading to dementia (see Chapter 611.4).

Regional cerebral hyperperfusion can be detected by single-photon emission CT studies and MR spectroscopy can detect focal areas of lactic acidosis in the brain. Neuropathology may show cortical atrophy with infarct-like lesions in both cortical and subcortical structures, basal ganglia calcifications, and ventricular dilation. Muscle biopsy specimens usually show RRF. Mitochondrial accumulations and abnormalities have been shown in smooth muscle cells of intramuscular vessels and of brain arterioles and in the epithelial cells and blood vessels of the choroid plexus, producing a mitochondrial angiopathy. Muscle biochemistry shows complex I deficiency in many cases; however, multiple defects have also been documented involving complexes I, III, and IV. Targeted molecular testing for specific mutations or sequence analysis and mutation scanning are generally used to make a diagnosis of MELAS when clinical evaluation suggests the diagnosis. Because the number of mutant genomes is lower in blood than in muscle, muscle is the preferable tissue for examination. Inheritance is maternal, and there is a highly specific, although not exclusive, point mutation at nt 3243 in the tRNA\textsuperscript{Leucine} gene of mtDNA in approximately 80% of patients. An additional 7.5% have a point mutation at nt 3271 in the tRNA\textsuperscript{Glu} gene. A third mutation has been identified at nt 3252 in the tRNA\textsuperscript{Leucine} gene. The prognosis in patients with the full syndrome is poor. Therapeutic trials reporting some benefit have included corticosteroids, coenzyme Q10, nicotinamide, carnitine, creatine, riboflavin and various combinations of these; t-arginine and preclinical studies reported some success with resveratrol.

MYOCLONUS EPILEPSY AND RAGGED RED FIBERS

MERRF syndrome is characterized by progressive myoclonic epilepsy, mitochondrial myopathy, and cerebellar ataxia with dysarthria and nystagmus. Onset may be in childhood or in adult life, and the course may be slowly progressive or rapidly downhill. Other features include dementia, sensorineural hearing loss, optic atrophy, peripheral neuropathy, and spasticity. Because some patients have abnormalities of deep sensation and pes cavus, the condition may be confused with Friedreich ataxia. A significant number of patients have a positive family history and short stature. This condition is maternally inherited.

Pathologic findings include elevated serum lactate concentrations, RRF on muscle biopsy, and marked neuronal loss and gliosis affecting, in particular, the dentate nucleus and inferior olivary complex with some dropout of Purkinje cells and neurons of the red nucleus. Pallor of the posterior columns of the spinal cord and degeneration of the gracile and cuneate nuclei occur. Muscle biochemistry has shown variable defects of complex III, complexes II and IV, complexes I and IV, or complex IV alone. More than 80% of cases are caused by a heteroplasmic G to A point mutation at nt 8344 of the tRNA\textsuperscript{Valine} gene of mtDNA. Additional patients have been reported with a T to C mutation at nt 8356 in the tRNA\textsuperscript{Valine} gene. Targeted mutation analysis or mutation analysis after sequencing of the mitochondrial genome is used to diagnosis MERRF.

There is no specific therapy, although coenzyme Q10 appeared to be beneficial in a mother and daughter with the MERRF mutation. The anticonvulsant levetiracetam is reported to help reduce myoclonus and myoclonic seizures in this disorder.

NEUROPATHY, ATAXIA, AND RETINITIS PIGMENTOSA SYNDROME

This maternally inherited disorder presents with either Leigh syndrome or with neurogenic weakness and NARP syndrome, as well as seizures. It is caused by a point mutation at nt 8993 within the ATPase subunit 6 gene. The severity of the disease presentation appears to have close correlation with the percentage of mutant mtDNA in leukocytes.
Two clinical patterns are seen in patients with NARP syndrome: (1) neuropathy, ataxia, retinitis pigmentosa, dementia, and ataxia, and (2) severe infantile encephalopathy resembling Leigh syndrome with lesions in the basal ganglia on MRI.

**LEBER HEREDITARY OPTIC NEUROPATHY**

LHON is characterized by onset usually between the ages of 18 and 30 yr of acute or subacute visual loss caused by severe bilateral optic atrophy, although children as young as 5 yr have been reported to have LHON. Three mtDNA mutations account for most cases of LHON and at least 85% of patients are young men. An X-linked factor may modulate the expression of the mtDNA point mutation. The classic ophthalmologic features include circumpapillary telangiectatic microangiopathy and pseudopapilledema of the optic disc. Variable features may include cerebellar ataxia, hyperreflexia, Babinski sign, psychiatric symptoms, peripheral neuropathy, or cardiac conduction abnormalities (preexcitation syndrome). Some cases are associated with widespread white matter lesions as seen with multiple sclerosis. Lactic acidosis and RRF tend to be conspicuously absent in LHON. More than 11 mtDNA point mutations have been described, including a usually homoplasmic G to A transition at nt 11,778 of the ND4 subunit gene of complex I. The latter leads to replacement of a highly conserved arginine residue by histidine at the 340th amino acid and accounts for 50-70% of cases in Europe and more than 90% of cases in Japan. Certain LHON pedigrees with other point mutations are associated with complex neurologic disorders and may have features in common with MELAS syndrome and with infantile bilateral striatal necrosis. One family has been reported with pediatric onset of progressive generalized dystonia with bilateral striatal necrosis associated with a homoplasmic G14459A mutation in the mtDNA ND6 gene, which is also associated with LHON alone and LHON with dystonia.

**KEARNS-SAYRE SYNDROME**

KSS is a characteristic multisystem disorder involving external ophthalmoplegia, heart block, and retinitis pigmentosa with onset before age 20 yr caused by single deletions in mtDNA. There must also be at least 1 of the following: heart block, cerebellar syndrome, or cerebrosplinal fluid protein >100 mg/dL. Other nonspecific but common features include dementia, sensorineural hearing loss, and multiple endocrine abnormalities, including short stature, diabetes mellitus, and hyperparathyroidism. The prognosis is guarded, despite placement of a pacemaker, and progressively downhill, with death resulting by the 3rd or 4th decade. Unusual clinical presentations can include renal tubular acidosis and Lowe syndrome. There are also a few overlap cases of children with KSS and stroke-like episodes. Muscle biopsy shows RRF and variable cytochrome c oxidase (COX)-negative fibers. Most patients have mtDNA deletions, and some have duplications. These may be new mutations accounting for the generally sporadic nature of KSS. A few pedigrees have shown autosomal dominant transmission. Patients should be monitored closely for endocrine abnormalities, which can be treated. Coenzyme Q is reported anecdotally to have some beneficial effect; a positive effect of folinic acid for low folate levels also is reported. A report of positive effects of a cochlear implant for deafness is also reported.

Sporadic progressive external ophthalmoplegia with ragged red fibers is a clinically benign condition characterized by adolescent or young adult—onset ophthalmoplegia, ptosis, and proximal limb girdle weakness. It is slowly progressive and compatible with a relatively normal life. The muscle biopsy material demonstrates RRF and COX-negative fibers. Approximately 50% of patients with progressive external ophthalmoplegia have mtDNA deletions, and there is no family history.

**REVERSIBLE INFANTILE CYTOCHROME C OXIDASE DEFICIENCY MYOPATHY**

Mutations in mtDNA are also responsible for a reversible form of severe neuromuscular weakness and hypotonia in infants that is the result of a maternally inherited homoplasmic m.14674T>C mt-tRNA_{mth} mutation associated with a deficiency of COX. Affected children present within the 1st few wk of life with hypotonia, severe muscle weakness, and very elevated serum lactate levels, and they often require mechanical ventilation. However, feeding and psychomotor development are not affected. Muscle biopsies taken from these children in the neonatal period show RRF and deficient COX activity, but these findings disappeared within 5-20 mo when the infants recovered spontaneously. It is difficult to distinguish these infants from those with lethal mitochondrial disorders without waiting for them to improve. The mechanism for this recovery is not established, but it may reflect a developmental switch in mitochondrial RNAs later in infancy. This reversible disorder is observed only in COX deficiency associated with the 16474T>C mt-tRNA_{mth} mutation, so it is suggested that infants with this type of severe weakness in the neonatal period be tested for this mutation to help with prognosis.

**LEIGH DISEASE (SUBACUTE NECROTIZING ENCEPHALOMYOPATHY)**

Leigh disease is a progressive degenerative disorder presenting in infancy with feeding and swallowing problems, vomiting, and failure to thrive associated with lactic acidosis and lesions seen in the brainstem and/or basal ganglia on MRI (Table 598-3). There are several genetically determined causes of Leigh disease that result from nuclear DNA mutations in genes that code for components of the respiratory chain: pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10. These defects may occur sporadically or be inherited by autosomal recessive transmission, as in the case of COX deficiency; by X-linked transmission, as in the case of pyruvate dehydrogenase E1α deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. Approximately 30% of cases are caused by mutations in mtDNA. Delayed motor and language milestones may be evident, and generalized seizures, weakness, hypotonia, ataxia, tremor, pyramidal signs, and nystagmus are prominent findings. Intermittent respirations with associated sighing or sobbing are characteristic and suggest brainstem dysfunction. Some patients have external ophthalmoplegia, ptosis, retinitis pigmentosa, optic atrophy, and decreased visual acuity. Abnormal results on CT or MRI scan consist of bilaterally symmetric areas of low attenuation in the basal ganglia and brainstem as well as elevated lactic acid on MR spectroscopy (Fig. 598-3). Pathologic changes consist of focal symmetric areas of necrosis in the thalamus, basal ganglia, tegmental gray matter, periventricular and periaqueductal regions of the brainstem, and posterior columns of the spinal cord. Microscopically, these spongiform lesions show cystic cavitation with neuronal loss, demyelination, and vascular proliferation. Elevations in serum lactate levels are characteristic and hypertrophic cardiomyopathy, hepatic failure and renal tubular dysfunction can occur. The overall outlook is poor, but a few patients experience prolonged periods of remission. There is no definitive treatment for the underlying disorder, but a range of vitamins including riboflavin, thiamine, and coenzyme Q are often given to try to improve mitochondrial function. Biotin, creatine, succinate, and idebenone, as well as a high-fat diet have also been used, but phenobarbital and valproic acid should be avoided because of their inhibitory effect on the mitochondrial respiratory chain.

**REYE SYNDROME**

This encephalopathy, which has become uncommon, is associated with pathologic features characterized by fatty degeneration of the viscera (microvesicular steatosis) and mitochondrial abnormalities and biochemical features consistent with a disturbance of mitochondrial metabolism (see Chapter 361).

Recurrent Reye-like syndrome is encountered in children with genetic defects of fatty acid oxidation, such as deficiencies of the plasma-membrane carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase, medium- and long-chain acyl-coenzyme A dehydrogenase, multiple acyl-coenzyme A dehydrogenase, and long-chain 3-hydroxyacyl-coenzyme A dehydrogenase or trifunctional protein. These disorders are manifested by recurrent hypoglycemic and hypoketotic encephalopathy, and they are inherited
Table 598-3  Clinical Features of Congenital Leigh Syndrome or Leigh-Like Syndrome

<table>
<thead>
<tr>
<th>Neurologic Manifestations</th>
<th>Nonneurologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>Dysmorphic Features</td>
</tr>
<tr>
<td>Bradynea, hypopnea, episodes of apnea</td>
<td>Lip cleft</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Short distal phalanges</td>
</tr>
<tr>
<td>Tetraparesis</td>
<td>Single palmar crease</td>
</tr>
<tr>
<td>Hypotonia (floppy infant)</td>
<td>Rostral vertebrae</td>
</tr>
<tr>
<td>Failure to thrive, poor sucking</td>
<td>Round face</td>
</tr>
<tr>
<td>Swallowing difficulties, dysphagia, poor feeding, poor sucking</td>
<td>Frontal bossing</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Flat nasal root</td>
</tr>
<tr>
<td>Spasticity, brisk tendon reflexes</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>Dysphasia, dysarthria</td>
<td>Thin lips</td>
</tr>
<tr>
<td>Squint</td>
<td>Small chin</td>
</tr>
<tr>
<td>Absence of optic or acoustic blink</td>
<td>Long, featureless philtrum</td>
</tr>
</tbody>
</table>

Other Cerebral Manifestations
- Stroke-like episodes
- Delay of developmental milestones
- Paralysis of vertical gaze
- Myoclonic jerks of limbs or eyelids
- Hypothermia
- Drowsiness, dizziness
- Psychomotor (mental) retardation
- Ataxia, tremor
- Seizures, convulsions
- Growth retardation
- Dystonia
- Clumsiness, dullness
- Nystagmus, uncoordinated eye movement, slow saccades
- Optic atrophy
- Visual loss
- Facial dyskinesia
- Ocular apraxia
- Drooling
- Gaze fixation difficulty

Peripheral Nervous System Manifestations
- Cranial nerve palsies
- Generalized wasting
- Bilateral ptoses
- Chronic progressive external ophthalmoplegia, strabismus
- Reduced tendon reflexes
- Polyneuropathy
- Muscle weakness
- Myopathy


Figure 598-3 Leigh syndrome. Axial T2-weighted magnetic resonance images (TR/TE/NEX = 3,000/120/1 msec) of 8 mo old girl with Leigh syndrome because of a SURF1 mutation indicate hyperintense lesions in substantia nigra and medial thalamic nuclei (A, B). Follow-up images (TR/TE/NEX = 2,028/120/2 msec) at age 26 mo (C) indicate hyperintense putamina and hyperintense left caudate nucleus. (From Farina L, Chiapparini L, Uziel G, et al: MR findings in Leigh syndrome with COX deficiency and SURF-1 mutations, AJNR Am J Neuroradiol 23:1095–1100, 2002, Fig. 2.)
in an autosomal recessive pattern. Other potential inborn errors of metabolism presenting with Reye syndrome include urea cycle defects (ornithine transcarbamylase, carbamyl phosphate synthetase) and certain of the organic acidurias (glutaric aciduria type I), respiratory chain defects, and defects of carbohydrate metabolism (fructose intolerance).

Bibliography is available at Expert Consult.

### 598.3 Other Encephalopathies

#### HIV ENCEPHALOPATHY

Encephalopathy is an uncommon and common manifestation in infants and children with HIV infection (see Chapter 276).

#### LEAD ENCEPHALOPATHY

See Chapter 721.

#### BURN ENCEPHALOPATHY

An encephalopathy develops in approximately 5% of children with significant burns in the 1st several wk of hospitalization (see Chapter 75). There is no single cause of burn encephalopathy but rather a combination of factors that include anoxia (smoke inhalation, carbon monoxide poisoning, laryngospasm), electrolyte abnormalities, bacte-

#### HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is most commonly associated with renal disease in children, including acute glomerulonephritis, chronic pyelo-

#### RADIATION ENCEPHALOPATHY

Acute radiation encephalopathy is most likely to develop in young patients who have received large daily doses of radiation. Excessive radiation injures vessel endothelium, resulting in enhanced vascular permeability, cerebral edema, and numerous hemorrhages. The child may suddenly become irritable and lethargic, complain of headache, or present with focal neurologic signs and seizures. Patients occasion-

<table>
<thead>
<tr>
<th>Table 598-4 Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute encephalopathy following (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.</td>
</tr>
<tr>
<td>2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein.</td>
</tr>
<tr>
<td>3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla. No involvement of other central nervous system regions.</td>
</tr>
<tr>
<td>4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.</td>
</tr>
<tr>
<td>5. Exclusion of resembling diseases.</td>
</tr>
<tr>
<td>A. Differential diagnosis from clinical viewpoints. Overwhelming bacterial and viral infections, and fulminating hepatitis; toxic shock, hemolytic uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.</td>
</tr>
<tr>
<td>B. Differential diagnosis from radiologic viewpoints. Legh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma.</td>
</tr>
</tbody>
</table>


#### ACUTE NECROTIZING ENCEPHALOPATHY

Acute necrotizing encephalopathy is a rare, severe encephalopathy seen more commonly in Asian countries. It is thought to be triggered by a viral infection (influenza, HHV-6) in a genetically susceptible host. Table 598-4 lists the diagnostic criteria. The elevation of hepatic enzymes without hyperammonemia is a unique feature. A familial or recurrent form is associated with mutations in the RANBP2 gene and is designated ANE1. MRI finding are characterized by symmetric lesions that must be present in the thalami (Fig. 598-4). The prognosis is usually poor, however some patients have responded to steroids and intravenous immunoglobulin (IVIG).

#### CYSTIC LEUKOENCEPHALOPATHY

An autosomal recessive disorder caused by mutations of RNASET2 proteins produces a brain MRI study that closely resembles congenital cytomegalovirus infection. Cystic leukoencephalopathy is manifest as a static encephalopathy without megalencephaly.
Bibliography


Bibliography


Encephalopathies

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Figure 598-4 Acute necrotizing encephalopathy. MRI at presentation. A, Axial diffusion-weighted image; B, axial apparent diffusion coefficient (ADC) map; C, axial T2-weighted image; D, axial fluid-attenuated inversion recovery (FLAIR) image; E, contrast-enhanced axial T1-weighted image; F, axial susceptibility weighted image. Diffusion-weighted images (A) and corresponding ADC map (B) clearly show multiple areas of restricted diffusion against a background of increased diffusion involving both thalami, which are swollen. On T2-weighted (C) and FLAIR (D) images, the thalami are markedly swollen and hyperintense. On T1-weighted images obtained after intravenous gadolinium chelate injection (E), multiple necrotic portions are well delineated by peripheral faint, linear enhancement. Incidental choroid plexus cysts are detected. Susceptibility weighted image (F) shows multiple hypointense spots, consistent with petechial hemorrhage. (From Bergamino L, Capra V, Biancheri R, et al: Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: is it useful? Brain Dev 34:384–391, 2012, Fig. 1.)

598.4 Autoimmune Encephalitis
Thaís Armangué and Josep O. Dalmau

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 yr to adult) but preferentially affect younger adults and children (Table 598-5). These disorders associate with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity, or neuronal excitability. The syndromes vary according to the associated antibody with phenotypes that resemble those in which the function of the target antigen is pharmacologically or genetically modified.

Most of these disorders are severe and potentially fatal but patients frequently respond to immunotherapy with good outcomes. Moreover, because of the broad spectrum of symptoms—including alterations of behavior, psychosis, catatonia, memory deficits, seizures, abnormal movements, and autonomic dysregulation—patients usually require a multidisciplinary treatment approach often in an intensive care unit.

The identification of these disorders provides a definitive diagnosis to many cases of encephalitis previously considered idiopathic, infectious, or postinfectious, although no causative agents were found. Because the etiology and pathogenic mechanisms were unknown, some of these disorders were previously defined with descriptive terms. More than half of cases under the ill-defined term “encephalitis lethargica” and some cases of “choreoathetosis post–herpes simplex encephalitis” are known to be anti–N-methyl-d-aspartate receptor (NMDAR) encephalitis.

The mechanisms that trigger the production of the antibodies are unknown. In a small subgroup of adolescent or young adult patients, the presence of a tumor that expresses the target neuronal antigen likely contributes in triggering the immune response. In addition, the high prevalence of prodromal viral-like symptoms has suggested that nonspecific viral infections may contribute to breaking immune tolerance and increase the permeability of the blood–brain barrier to antibodies. Nonetheless in many of these disorders the blood–brain barrier appears intact and there is evidence that the autoantibodies are
### Autoimmune Encephalitis in Children

<table>
<thead>
<tr>
<th>MECHANISMS</th>
<th>TUMOR ASSOCIATION</th>
<th>SYNDROME</th>
<th>ANCILLARY TEST</th>
<th>TREATMENT/PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-NMDAR ENCEPHALITIS</strong></td>
<td>Antibodies against NR1 subunit of NMDAR, disrupt function by crosslinking and internalization of receptors</td>
<td>Age and gender related: 41% in females older than 12 yr; &lt;6% in girls younger than 12 yr. No tumors identified in young boys</td>
<td>Psychiatric symptoms, seizures, orofacial dyskinesias and other abnormal movements, autonomic dysfunction</td>
<td>EEG: almost always abnormal; it may show “extreme delta brush” pattern. Brain MRI: nonspecific findings in ~35%. CSF: pleocytosis and/or increased protein in &gt;80%.</td>
</tr>
<tr>
<td><strong>LIMBIC ENCEPHALITIS</strong></td>
<td>Antibodies against intraneuronal antigens: Hu, Ma2, amphiphysin, GAD</td>
<td>Extremely rare in children (see text)</td>
<td>Severe short-term memory loss, seizures</td>
<td>EEG: temporal lobe epileptic activity; focal or generalized slowing MRI: increased T2 and FLAIR signal in limbic region CSF: pleocytosis and increased proteins</td>
</tr>
<tr>
<td><strong>BICKERSTAFF ENCEPHALITIS</strong></td>
<td>GQ1b antibodies</td>
<td>No tumor association</td>
<td>Ophthalmoplegia, ataxia, hyperreflexia. May overlap with Miller-Fisher syndrome</td>
<td>MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~44% (predominant axonal degeneration, less frequent demyelination) CSF abnormalities suggesting B-cell activation MRI: in some cases cerebellar atrophy MRI: normal in ~48% hypothyroidism, MRI often normal EEG: slow activity, CSF: elevated protein</td>
</tr>
<tr>
<td><strong>HASHIMOTO ENCEPHALITIS</strong></td>
<td>TPO antibodies</td>
<td>No tumor association</td>
<td>Stroke-like symptoms, tremor, myoclonus, aphasia, sleep and behavioral problems seizures, ataxia</td>
<td>MRI: abnormal in ~30% Hypothyroidism, MRI often normal EEG: slow activity, CSF: elevated protein</td>
</tr>
<tr>
<td><strong>RASMUSSEN ENCEPHALITIS</strong></td>
<td>Most likely immune mediated (unclear mechanism)</td>
<td>No tumor association</td>
<td>Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy</td>
<td>MRI: progressive unilateral hemispheric atrophy MRI: normal in ~48% hypothyroidism, MRI often normal EEG: slow activity, CSF: elevated protein</td>
</tr>
<tr>
<td><strong>BASAL GANGLIA ENCEPHALITIS</strong></td>
<td>Antibodies to D2R in some cases</td>
<td>No tumor association</td>
<td>Abnormal movement and behavior disorder</td>
<td>Variable basal ganglia T2/FLAIR abnormalities</td>
</tr>
<tr>
<td><strong>POSSIBLE IMMUNE MECHANISMS</strong></td>
<td>CLIPPERS</td>
<td>No antibodies</td>
<td>No tumor association</td>
<td>Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction</td>
</tr>
<tr>
<td></td>
<td>ROHHAD</td>
<td>Unknown. Autoimmune and genetic origin postulated.</td>
<td>Neural crest tumor in ~50% of cases</td>
<td>Rapid onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypothyelination</td>
</tr>
</tbody>
</table>

*Includes rituximab and cyclophosphamide.

†Exact frequency is unknown.

CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; GABAAR, γ-aminobutyric acid-B receptor; GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase.
synthesized within the CNS by plasma cells that form part of local brain and meningeal inflammatory infiltrates.

**ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS**

In this disorder, the antibodies target the NR1 subunit of the NMDA receptor. The exact frequency of this syndrome is unknown but it is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis in children and adolescents. Overall, the disorder predominates in females (80%), although in patients younger than 12 yr the frequency of males is higher (40%). The resulting syndrome is highly predictable and usually evolves in stages. In teenagers and young adults, the disorder usually presents with prominent psychiatric manifestations that may include rapidly progressive anxiety, agitation, delusional thoughts, bizarre behavior, labile affect, mood disturbances (mania), catatonic features, memory deficit, language disintegration, aggression, and insomnia or other sleep disturbances. In many cases, these symptoms had been preceded by a few days of prodromal headache, fever or viral-like symptoms. As a result of this symptom presentation, patients are often misdiagnosed with new-onset psychosis or a primary psychiatric disorder. However, in a few days or weeks, additional symptoms occur, including a decreased level of consciousness, seizures (including status epilepticus), limb or oral dyskinesias, choreoathetoid movements, and autonomic instability which usually includes tachycardia, bradycardia, fluctuations of blood pressure, hypoventilation, hyperthermia and sialorrhea. In rare instances, bradycardia and cardiac pauses occur, at times requiring the transient use of a pacemaker. The disorder also occurs in toddlers and infants (the youngest patient identified to date was 6 mo old), and although the evolution of the syndrome is similar to that of adults, young patients more frequently present with motor or complex seizures and movement disorders. Because of their age, the psychiatric–behavioral features may be missed. In this young age group, behavior changes include irritability, new-onset temper tantrums, agitation, aggression, reduced speech, mutism, and autistic-like regression. Moreover, compared with adults some children also develop cerebellar ataxia and hemiparesis; in contrast, autonomic dysfunction is usually milder and less severe in children. There is often an abrupt on–off phenomenon in alterations of responsiveness or level of consciousness.

Brain MRI is abnormal in approximately 35% of cases, usually showing nonspecific cortical and subcortical T2-fluid-attenuated inversion recovery (FLAIR) signal abnormalities, sometimes with transient cortical or meningeal enhancement; nonspecific white matter abnormalities are common. Lesions may also involve the spinal cord producing symptoms of myelitis. The cerebrospinal fluid (CSF) is initially abnormal in approximately 80% of cases, showing moderate lymphocytic pleocytosis and less frequently increased protein synthesis and oligoclonal bands. The electroencephalogram (EEG) is abnormal in virtually all patients, and usually shows focal or diffuse slow activity in the delta and theta range, which does not correlate with abnormal movements. In addition, many patients develop epileptic activity, requiring video-monitoring for adequate clinical management. A characteristic EEG pattern called “extreme delta brush” characterized by beta-delta complexes occurs in 30% of adults and has been described in children (Fig. 598-5).

The diagnosis of the disorder is established by demonstrating NMDAR antibodies in CSF or serum. The sensitivity is higher in CSF compared with serum (100% vs 85%), and the levels of antibodies in CSF appear to correlate better with outcome. Antibodies may remain detectable, albeit at lower titers, after patients recover.

The presence of an underlying tumor, mostly teratomas, is age and sex dependent. Whereas 40% of females older than 12 yr have an underlying teratoma of the ovary, less than 6% of females younger than 12 yr have a tumor. In young boys with anti-NMDAR encephalitis, the presence of an underlying tumor is exceptional; in young adults, the presence of a testicular teratoma is also rare (<15% of cases). In children, MRI of abdomen and pelvis and abdominal and testicular ultrasound are the preferred tumor screening tests.

In a small number of patients, anti-NMDAR encephalitis occurs simultaneously or after infections with a variety of pathogens, including *Mycoplasma pneumoniae*, human herpes simplex viruses 1 and 6 (HSV), enterovirus, and influenza. A pathogenic link with most of these infections has not established; there is evidence that some patients with HSV encephalitis develop antibodies against the NR1 subunit of the NMDAR. These patients may progress to develop relapsing neurologic symptoms post-HSV encephalitis. In a subgroup of patients with noninfectious relapsing neurologic symptoms post-HSV encephalitis, or “choreoathetosis post-HSV encephalitis,” the disorder is in fact anti-NMDAR encephalitis (see Videos 598-1, 598-2, and 598-3).

Although no prospective clinical trials have been done, there is evidence that tumor removal, when appropriate, and prompt immunotherapy improve outcome. Most children receive first-line immunotherapies, including corticosteroids, IVIG, or plasma exchange. However, because these treatments fail in almost 50% of patients, and with an increasing number of reports showing that rituximab can be effective, this treatment is increasingly being used in combination with IVIG and steroids, or after first-line immunotherapies. Cyclophosphamide can be effective when there has been no response to these treatments.

Although anti-NMDAR encephalitis has a mortality rate of 7%, approximately 80% of patients have substantial or full recovery. Recovery is usually slow and can take as long as 2 yr after symptom onset. The last symptoms to improve are social interactions, and language and executive functions. Relapses occur in approximately 15% of patients; they can develop as partial syndromes, are usually milder than the initial episode and respond equally to immunotherapy. Initial comprehensive immunotherapy appears to prevent or reduce the number of relapses. The efficacy of chronic immunosuppression with drugs such as azathioprine or mycophenolate mofetil in preventing relapses is unknown.

The differential diagnosis of anti-NMDAR encephalitis is extensive and varies according to the stage of the disease (Table 598-6). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug abuse.

**LIMBIC ENCEPHALITIS**

This disorder refers to an inflammatory process of the limbic system including, the medial temporal lobes, amygdala, and cingulate gyri. In adults, the most frequent immune-mediated limbic encephalitis occurs...
## Differential Diagnosis of Anti-NMDAR Encephalitis in Children

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral encephalitis</td>
<td>Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.</td>
</tr>
<tr>
<td>Relapsing post-herpes simplex virus encephalitis</td>
<td>Occurs ~4-6 wk after successful treatment of herpes simplex encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir), or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.</td>
</tr>
<tr>
<td>New-onset psychosis</td>
<td>Because most patients with anti-NMDAR encephalitis present with psychosis, a primarily psychiatric disorder is frequently considered. As the disease evolves, the development of neurological symptoms usually reveals the diagnosis.</td>
</tr>
<tr>
<td>Drugs/toxins</td>
<td>The acute development of personality and behavioral changes, and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug abuse (e.g., ketamine, phencyclidine, among others). Carbon monoxide.</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>The occurrence of altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.</td>
</tr>
<tr>
<td>Encephalitis lethargica</td>
<td>This is an ill-defined entity, likely representing multiple disorders. Criteria include: acute or subacute encephalitis with at least 3 of the following signs: signs of basal ganglia involvement; oculogyric crises; opthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Approximately, 50% of patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.</td>
</tr>
<tr>
<td>Childhood disintegrative disorder/late-onset autism</td>
<td>Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. While the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have substantial clinical recovery.</td>
</tr>
<tr>
<td>Kleine-Levin syndrome</td>
<td>Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and child-like behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis, or as permanent sequelae.</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson, and Lesch-Nyhan syndromes. Pantothenate kinase associated neurodegeneration, porphyria, and urea cycle defects should also be considered.</td>
</tr>
<tr>
<td>Monoamine neurotransmitter disorders</td>
<td>Deficiency of dopamine, serotonin or both can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.</td>
</tr>
<tr>
<td>Demyelinating disorders</td>
<td>Acute disseminated encephalomyelitis and neuromyelitis optica are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMO the presence of aquaporin 4 antibodies in serum or CSF is associated with relapses and poor prognosis.</td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>CNS vasculitis results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large vessel angiitis, and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter, not restricted to vascular territories with frequent leptomeningeal and/or local enhancement.</td>
</tr>
<tr>
<td>Systemic rheumatic disorders</td>
<td>Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.</td>
</tr>
</tbody>
</table>

CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; LE, limbic encephalitis; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; NMO, neuromyelitis optica; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction.
in association with antibodies against proteins that were once thought to be voltage-gated potassium channels (VGKC), but which, in fact, target a secreted neuronal protein called leucine-rich glioma-inactivated 1 (LG1), and a protein called Caspr2 expressed in brain and juxtaparanodal regions of myelinated nerves. Patients with LG1 antibody associated limbic encephalitis often develop hyponatremia; in some patients the disorder is preceded by short-lasting episodes of distinctive dystonic or myoclonic-like movements, described as factitio-brachial dystonic seizures, but with EEG features of tonic seizures. Patients with antibodies to Caspr2 usually develop Morvan syndrome, which includes encephalopathy, seizures, autonomic dysfunction, and neuromyotonia. How the clinical significance of antibodies called "VGKC-complex proteins" differs from LG1 and Caspr2 is unknown.

Other less frequent types of autoimmune limbic encephalitis in adults are paraneoplastic and may occur with antibodies against intracellular antigens (e.g., Hu, CRMP5, Ma2) or neuronal cell surface and synaptic proteins (e.g., AMPA, GABA_A receptor, mGlur5). While the disorders associated with antibodies against intracellular antigens appear to be mediated by cytotoxic T-cell responses and are poorly responsive to treatment, those associated with antibodies to cell surface and synaptic antigens are likely mediated by the antibodies and treatment responsive.

In children, autoimmune or paraneoplastic limbic encephalitis is exceptional. Unfortunately, any type of encephalopathy resulting in seizures and alteration of memory and behavior is frequently labeled as "limbic encephalitis," making data based on literature searches using the term "limbic encephalitis" unreliable. Fewer than 30 children with limbic encephalitis have been described in the English literature, some of them with antibodies against intracellular or cell surface antigens (Hu, Ma2, GAD, amphiphysin, GABA_A, and VGKC-complex proteins different from LG1 and Caspr2). In some cases an underlying tumor was identified and included, leukemia, ganglioneuroblastoma, neuroblastoma, and small-cell carcinoma of the ovary.

The Ophelia syndrome is a form of limbic encephalitis that occurs in association with Hodgkin’s lymphoma and predominantly affects young adults, teenagers or children. Some patients develop antibodies against mGlur5, a receptor involved in learning and memory; symptoms are usually responsive to chemotherapy.

HASHIMOTO ENCEPHALOPATHY
Hashimoto encephalopathy is defined by the detection of thyroid peroxidase (TPO) antibodies in patients with acute or subacute encephalitis that responds to corticosteroids. Since almost 50% of patients have normal thyroid function and not all patients respond to steroids, the term “encephalopathy associated with autoimmune thyroid disease” is considered more accurate than the previous term “steroid-responsive encephalopathy associated with autoimmune thyroiditis.” Clinical features are not specific and may include stroke-like symptoms, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The CSF usually shows elevated protein level with less-frequent pleocytosis. EEG studies almost always are abnormal frequently showing generalized slowing. Brain MRI is usually normal, although it may show diffuse white matter abnormalities and meningeal enhancement that can resolve with steroid therapy. As TPO antibodies occur in approximately 10% of asymptomatic children (nonencephalopathic and most cases euthyroid), as well as in patients who have more relevant antibody-associated disorders, such as GABA_A, LG1, or NMDAR antibodies, TPO antibodies should be viewed as a marker of autoimmunity rather than a neurologic disease-specific or pathogenic antibody. Importantly the presence of TPO antibodies should not prevent testing for more relevant antibodies.

OPSOCLONUS–MYOCLONUS AND OTHER BRAINSTEM–CEREBELLAR ENCEPHALITIDIES
Opsoclonus-myoclonus occurs in infants, teenagers and adults, although it probably represents different diseases and pathogenic mechanisms. In infants, the syndrome usually develops in the 1st 2 yr of life (mean: 20 mo), and at least 50% of patients have an underlying neuroblastoma. The child often presents with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms may include refusal to walk or sit, speech problems, hyponatremia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients may initially be diagnosed with acute cerebellitis or labyrinthitis. Typically CSF abnormalities suggest B-cell activation, and the presence of antibodies against neuronal proteins has been demonstrated in several studies, although the identification of a specific autoantigen has been elusive.

Immunosuppressive treatment, including corticosteroids, IVIG, rituximab, and cyclophosphamide often improves the abnormal eye movements, but residual behavioral, language, and cognitive problems persist in the majority of patients, often requiring special education. In addition, insomnia and abnormal response to pain are common. Relapses occur in 50% of the patients, usually as a result of an intercurrent infection or drug tapering. Delay in treatment appears to associate with a poorer neurologic outcome; therefore, in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.

In teenagers and young adults, opsoclonus–myoclonus and brainstem–cerebellar encephalitis without opsoclonus are often considered “idiopathic” or “postinfectious”; however, there is evidence that some of these patients have an underlying teratoma, usually in the ovaries. These patients do not harbor NMDAR antibodies, and compared with those with anti-NMDAR encephalitis are less likely to initially present with psychosis and behavioral changes, and rarely develop dyskinesias. Although these patients do not appear to have neuronal antibodies, the CSF often shows pleocytosis and elevated protein concentration. Identification of this subphenotype of opsoclonus–myoclonus is important because patients usually have full recovery after treatment with immunotherapy (corticosteroids, IVIG, and/or plasma exchange) and if present, removal of the ovarian teratoma. The prognosis of this disorder seems better than that of neuroblastoma-associated opsoclonus, or the paraneoplastic opsoclonus of older patients, usually related to breast, ovarian, or lung cancer.

BICKERSTAFF ENCEPHALITIS
This term is used to describe patients with subacute progressive ophthalmoplegia and ataxia in addition to drowsiness or hyperreflexia. Although this entity has been described more frequently in adults, children as young as 3 yr old have been identified. Most patients are treated with steroids, IVIG, and/or plasma exchange, and often have good outcome. Serum GQ1b immunoglobulin G antibodies are found in 66% of patients. Brain MRI abnormalities occur in 30% of the patients and usually include increased T2-signal abnormalities in the brainstem, thalamus, cerebellum, and sometimes cerebral white matter. Some patients develop hyporeflexia and limb weakness, with predominate axonal involvement, overlapping with symptoms of the Miller–Fisher syndrome and the axonal subtype of the Guillain-Barré syndrome.

CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS
This is a clinically and radiologically distinct pontine-predominant encephalomyelitis. To date fewer than 30 patients have been reported and two of them were children (13 and 16 yr). Patients usually present with episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction. Brain MRI shows symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain and occasionally spinal cord. The clinical and radiological findings usually respond to high dose steroids but may worsen after the steroid taper, requiring chronic steroid or other immunosuppressive therapy. The differential diagnosis is extensive and includes infections, granulomatous disease, lymphoma or vasculitis. Biopsy studies may be needed to exclude these and other conditions.
**AUTOIMMUNE ENCEPHALOPATHIES ASSOCIATED WITH EPILEPSY AND STATUS EPILEPTICUS**

**Rasmussen encephalitis** is an inflammatory encephalopathy characterized by progressive refractory partial seizures, cognitive deterioration, and focal deficits that occur with gradual atrophy of 1 brain hemisphere. The disorder frequently presents in 6–8 yr old children, although adolescents and adults can be affected. The etiology is unknown and, therefore, multiple theories are proposed, including the presence of antibodies against the GluR3 subunit of the AMPA receptor and T-cell mediated mechanisms triggered by a viral infection. None of these mechanisms satisfactorily explains the unilateral brain involvement characteristic of the disorder. Treatment with high-dose steroids, plasma exchange, or IVIG can ameliorate symptoms in early stages of the disease. Rituximab and intraventricular γ-interferon have been effective in a few isolated cases. In a small series, patients treated with tacrolimus showed better outcomes of neurologic function and slower progression of cerebral hemiatrophy, but not improved seizure control. The only definitive treatment is functional hemispherectomy that consists in surgical disconnection of the affected hemisphere.

The discovery of treatment-responsive encephalitis associated with antibodies against cell surface or synaptic proteins has resumed the interest for a potential autoimmune basis of several devastating encephalopathies with refractory seizures. Some well-defined autoimmune encephalitis such as **anti-NMDAR encephalitis**, which presents in children with refractory seizures or status epilepticus. In these patients, the development over a short period of time of the characteristic spectrum of symptoms (altered behavior, orofacial dyskinesias, and autonomic dysfunction) and demonstration of NMDAR antibodies leads to the correct diagnosis and initiation of immunotherapy.

A devastating epileptic encephalopathy associated with fever named **fever-induced refractory epileptic encephalopathy syndrome**, among other terms, is suspected to be an infection-triggered autoimmune process because of its biphasic clinical course and the occasional finding of neuronal antibodies in a few patients. However, the lack of response to most treatments including immunotherapy, and the rare and inconsistent association to different types of antibodies cast doubts on an autoimmune pathogenesis. Other investigators suggest a genetic error in metabolism.

Antibodies to VGKC-complex proteins different from LGI1 and Caspr2 have been described in a few children with encephalitis with or without status epilepticus. Given that the target antigens are unknown and the response to immunotherapy is unpredictable, the significance of these antibodies is unclear.

**OTHER SUSPECTED AUTOIMMUNE ENCEPHALITIDES**

Demyelinating disorders, vasculitis of the CNS, and rheumatic diseases associate with autoimmune mechanisms can result in encephalitis.

Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) usually affects children who had normal development until 2-4 yr of age and then develop rapid onset of hyperphagia, weight gain, and abnormal behavior (social disinhibition, irascibility, impulsivity, lethargy, outburst of euphoria and laughing, impaired concentration), followed by autonomic dysfunction (abnormal pupillary responses, thermal dysregulation, gastrointestinal dysmotility), and central hypoventilation. An autoimmune or paraneoplastic etiology of ROHHAD syndrome is supported by the frequent association to neural crest tumors, the identification in some patients of genetic factors predisposing to autoimmunity, and the finding of intrathecal oligoclonal bands and infiltrates of lymphocytes and histiocytes in the hypothalamus of some patients. Furthermore, responses to immunotherapy have been described in a few patients. A possible genetic origin is suggested because of the similarities of this syndrome with the congenital central hypoventilation syndrome (Ondine curse) related to a **PHOX2B** mutation, which presents in the neonatal period and also associates with autonomic problems (Hirschsprung disease) and neural crest tumors (see Chapter 418.2). However, no mutations in **PHOX2B** and other candidate genes have been found in patients with ROHHAD.

The term **basal ganglia encephalitis** is used to describe patients with predominant or isolated involvement of the basal ganglia. These patients typically have abnormal movements and neuropsychiatric disease. Although these disorders probably have multiple etiologies, including metabolic, toxic, genetic, and infectious processes, an immune-mediated etiology has been postulated in some patients. There have been no clinical trials, but case reports and small noncontrolled case series describe the potential benefit of immunotherapy. Antibodies against the dopamine-2 receptor have been identified in some of these patients as well as in patients with Sydenham chorea and Tourette syndrome.

**Pseudomigraine syndrome with CSF pleocytosis (PMP) or head-ache with neurologic deficits and CSF lymphocytosis (HaNDL)** is an ill-defined entity that predominantly affects young male adults with a family history of migraine, although adolescents can be affected. This syndrome is characterized by repeated episodes of severe headache with transient neurologic deficits, accompanied by aseptic CSF lymphocytosis and normal brain MRI. Patients frequently show high CSF opening pressure, elevated CSF protein concentration, and focal EEG slowing, which normalize after the episodes of headache. Because of the inflammatory characteristics of the CSF and the high prevalence of prodromal viral-like symptoms, an infectious-autoimmune mediated mechanism has been proposed. Other theories include spreading cortical depression and trigeminal-vascular activation.

An immune-mediated mechanism and trigeminal-vascular activation are also considered as possible mechanisms of **ophthalmoplegic migraine**, also named **recurrent cranial neuralgia**. This disorder predominantly affects young children and is characterized by recurrent bouts of head pain in addition to cranial nerves III, IV, and/or VI involvement. In contrast to PMP/HaNDL, CSF studies do not show pleocytosis, and in approximately 75% of cases, the MRI shows focal nerve thickening and contrast enhancement. Observational data suggest that treatment with steroids may be beneficial. In this syndrome, as well as in PMP/HaNDL, the differential diagnosis includes structural, neoplastic, traumatic, metabolic, and infectious disorders.

**Bibliography is available at Expert Consult.**
Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases that result from specific genetic and biochemical defects, chronic viral infections, and varied unknown causes. Children with suspected neurodegenerative disorders were once subjected to brain and rectal (neural) biopsies, but with modern neuroimaging techniques and specific biochemical and molecular diagnostic tests, these invasive procedures are rarely necessary. The most important component of the diagnostic investigation continues to be a thorough history and physical examination. The hallmark of a neurodegenerative disease is regression and progressive deterioration of neurologic function with loss of speech, vision, hearing, or locomotion, often associated with seizures, feeding difficulties, and impairment of intellect. The age of onset, rate of progression, and principal...
neurologic findings determine whether the disease affects primarily the white or the gray matter. Upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders; convulsions and intellectual and visual impairments that occur early in the disease course are the hallmarks of gray matter disorders. A precise history and examination localizes the process within the nervous system. Although the outcome of a neurodegenerative condition is usually fatal and available therapies are often limited in effect, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented. Bone marrow transplantation and other novel therapies may prevent the progression of disease in certain individuals who are either presymptomatic or very early in their disease course. For all conditions in which the specific enzyme defect is known, prevention by prenatal diagnosis (chorionic villus sampling or amniocentesis) is possible. Carrier detection is also often possible by enzyme assay. Table 599-1 summarizes selected inherited neurodegenerative and metabolic disorders by their usual age of onset.

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**Table 599-1** Neurometabolic Conditions Associated with Developmental Regression

<table>
<thead>
<tr>
<th>AGE AT ONSET (yr)</th>
<th>CONDITIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 with hepatomegaly</td>
<td>Fructose intolerance</td>
<td>Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)</td>
</tr>
<tr>
<td></td>
<td>Galactosemia</td>
<td>Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)</td>
</tr>
<tr>
<td></td>
<td>Glycogenosis (glycogen storage disease) types I-IV</td>
<td>Hypoglycemia, cardiomegaly (type II)</td>
</tr>
<tr>
<td></td>
<td>Mucopolysaccharidosis types I and II</td>
<td>Coarse facies, stiff joints</td>
</tr>
<tr>
<td></td>
<td>Niemann-Pick disease, infantile type</td>
<td>Gray matter disease, failure to thrive</td>
</tr>
<tr>
<td></td>
<td>Tay-Sachs disease</td>
<td>Seizures, cherry-red macula, edema, coarse facies</td>
</tr>
<tr>
<td></td>
<td>Zellweger syndrome</td>
<td>Hypotonia, high forehead, flat faces</td>
</tr>
<tr>
<td></td>
<td>Gaucher disease (neuronopathic form)</td>
<td>Extensor posturing, irritability</td>
</tr>
<tr>
<td></td>
<td>Carbohydrate-deficient glycoprotein syndromes</td>
<td>Dysmyelination, cerebellar hypoplasia</td>
</tr>
<tr>
<td>&lt;2, without hepatomegaly</td>
<td>Krabbé disease</td>
<td>Irritability, extensor posturing, optic atrophy, and blindness</td>
</tr>
<tr>
<td></td>
<td>Rett syndrome</td>
<td>Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia</td>
</tr>
<tr>
<td></td>
<td>Maple syrup urine disease</td>
<td>Poor feeding, tremors, myoclonus, opisthotonos</td>
</tr>
<tr>
<td></td>
<td>Phenylketonuria</td>
<td>Light pigmentation, eczema, seizures</td>
</tr>
<tr>
<td></td>
<td>Menkes kinky hair disease</td>
<td>Hypertonia, irritability, seizures, abnormal hair</td>
</tr>
<tr>
<td></td>
<td>Subacute necrotizing encephalopathy of Leigh disease</td>
<td>White matter disease</td>
</tr>
<tr>
<td></td>
<td>Canavan disease</td>
<td>White matter disease, macrocephaly</td>
</tr>
<tr>
<td></td>
<td>Neurodegeneration with brain iron accumulation disease</td>
<td>White matter disease, movement disorder</td>
</tr>
<tr>
<td>2-5</td>
<td>Niemann-Pick disease types III and IV</td>
<td>Hepatosplenoomegaly, gait difficulty</td>
</tr>
<tr>
<td></td>
<td>Wilson disease</td>
<td>Liver disease, Kayser-Fleischer ring; deterioration of cognition is late</td>
</tr>
<tr>
<td></td>
<td>Gangliosidosis type II</td>
<td>Gray matter disease</td>
</tr>
<tr>
<td></td>
<td>Neuronal ceroid lipofuscinosis</td>
<td>Gray matter disease</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])</td>
<td>Gray matter disease</td>
</tr>
<tr>
<td></td>
<td>Ataxia-telangiectasia</td>
<td>Basal ganglia disease</td>
</tr>
<tr>
<td></td>
<td>Huntington disease (chorea)</td>
<td>Basal ganglia disease</td>
</tr>
<tr>
<td></td>
<td>Neurodegeneration with brain iron accumulation syndrome</td>
<td>Basal ganglia disease</td>
</tr>
<tr>
<td></td>
<td>Metachromatic leukodystrophy</td>
<td>Basal ganglia disease</td>
</tr>
<tr>
<td></td>
<td>Adrenoleukodystrophy</td>
<td>White matter disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>White matter disease, behavior problems, deteriorating school performance, quadriaparesis</td>
</tr>
<tr>
<td>5-15</td>
<td>Adrenoleukodystrophy</td>
<td>Same as for adrenoleukodystrophy in 2-5 yr olds</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>White matter disease</td>
</tr>
<tr>
<td></td>
<td>Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)</td>
<td>Gray matter disease</td>
</tr>
<tr>
<td></td>
<td>Schilder disease</td>
<td>White matter disease, focal neurologic symptoms</td>
</tr>
<tr>
<td></td>
<td>Refsum disease</td>
<td>Peripheral neuropathy, ataxia, retinitis pigmentosa</td>
</tr>
<tr>
<td></td>
<td>Sialidosis II, juvenile form</td>
<td>Cherry-red macula, myoclonus, ataxia, coarse facies</td>
</tr>
<tr>
<td></td>
<td>Subacute sclerosing panencephalitis</td>
<td>Diffuse encephalopathy, myoclonus; may occur years after measles</td>
</tr>
</tbody>
</table>


### 599.1 Sphingolipidoses

**Jennifer M. Kwon**

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes (Fig. 599-1). The sphingolipidoses are subclassified into 6 categories: Niemann-Pick disease, Gaucher disease, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease, and metachromatic leukodystrophy. Niemann-Pick disease and Gaucher disease are discussed in Chapter 86.4.

#### GANGLIOSIDOSIDOSIS

See also Chapter 86.4.

Gangliosides are glycosphingolipids, normal constituents of the neuronal and synaptic membranes. The basic structure of GM1 ganglioside consists of an oligosaccharide chain attached to a hydroxyl group of ceramide and sialic acid bound to galactose. The gangliosides are catabolized by sequential cleavage of the sugar molecules...
The Nervous System

Development is globally delayed, and generalized seizures are prominent. The phenotype is striking and shares many characteristics with Hurler syndrome. The facial features are coarse, the forehead is prominent, the nasal bridge is depressed, the tongue is large (macroglossia), and the gums are hypertrophied. Hepatosplenomegaly is present early in the course as a result of accumulation of foamy histiocytes, and kyphoscoliosis is evident because of anterior beaking of the vertebral bodies. The neurologic examination is dominated by apathy, progressive blindness, deafness, spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macular region is visualized in approximately 50% of cases. The cherry-red spot is characterized by an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea (Fig. 599-2). Children rarely survive beyond age 2-3 yr, and death may be from aspiration pneumonia.

Juvenile GM1 gangliosidosis has a delayed onset beginning about 1 yr of age. The initial symptoms consist of incoordination, weakness,

**Figure 599-1** Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

by specific exoglycosidases. Abnormalities in catabolism result in an accumulation of the ganglioside within the cell. Defects in ganglioside degradation can be classified into 2 groups: the GM1 gangliosidoses and the GM2 gangliosidoses.

**GM1 Gangliosidoses**
The 3 subtypes of GM1 gangliosidoses are classified according to age at presentation: infantile (type 1), juvenile (type 2), and adult (type 3). The condition is inherited as an autosomal recessive trait and results from a marked deficiency of acid β-galactosidase. This enzyme may be assayed in leukocytes and cultured fibroblasts. The acid β-galactosidase gene has been mapped to chromosome 3p14.2. Prenatal diagnosis is possible by measurement of acid β-galactosidase in cultured amniotic cells.

Infantile GM1 gangliosidosis presents at birth or during the neonatal period with anorexia, poor sucking, and inadequate weight gain. Development is globally delayed, and generalized seizures are prominent. The phenotype is striking and shares many characteristics with Hurler syndrome. The facial features are coarse, the forehead is prominent, the nasal bridge is depressed, the tongue is large (macroglossia), and the gums are hypertrophied. Hepatosplenomegaly is present early in the course as a result of accumulation of foamy histiocytes, and kyphoscoliosis is evident because of anterior beaking of the vertebral bodies. The neurologic examination is dominated by apathy, progressive blindness, deafness, spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macular region is visualized in approximately 50% of cases. The cherry-red spot is characterized by an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea (Fig. 599-2). Children rarely survive beyond age 2-3 yr, and death may be from aspiration pneumonia.

Juvenile GM1 gangliosidosis has a delayed onset beginning about 1 yr of age. The initial symptoms consist of incoordination, weakness,
ataxia, and regression of language. Thereafter, convulsions, spasticity, decerebrate rigidity, and blindness are the major findings. Unlike the infantile type, this type is not usually marked by coarse facial features and hepatosplenomegaly. Radiographic examination of the lumbar vertebrae may show minor beaking. Children rarely survive beyond 10 yr of age. Adult GM₁ gangliosidosis is a slowly progressive disease consisting of spasticity, ataxia, dysarthria, and a gradual loss of cognitive function.

**GM₂ Gangliosidoses**

The GM₂ gangliosidoses are a heterogeneous group of autosomal recessive inherited disorders that consist of several subtypes, including Tay-Sachs disease (TSD), Sandhoff disease, juvenile GM₂ gangliosidosis, and adult GM₂ gangliosidosis. TSD is most prevalent in the Ashkenazi Jewish population and has an approximate carrier rate of 1 in 30 Jews in the United States. TSD is caused by mutations in the HEXA gene located on chromosome 1q23-q24. Affected infants appear normal until approximately 6 mo of age, except for a marked startle reaction to noise that is evident soon after birth. Affected children then begin to lag in developmental milestones and, by 1 yr of age, they lose the ability to stand, sit, and vocalize. Early hypotonia develops into progressive spasticity, and relentless deterioration follows, with convulsions, blindness, deafness, and cherry-red spots in almost all patients (see Fig. 599-2). Macrocephaly becomes apparent by 1 yr of age and results from the 200-300-fold normal content of GM₂ ganglioside deposited in the brain. Few children live beyond 3-4 yr of age, and death is usually associated with aspiration or bronchopneumonia. A deficiency of the isoenzyme hexosaminidase A is found in tissues of patients with TSD. Mass screening for prenatal diagnosis of TSD is a reliable and cost-effective method of prevention because the condition occurs most frequently in a defined population (Ashkenazi Jews). Targeted screening is responsible for the fact that currently, the rare children with TSD born in the United States are most commonly born to non-Jewish parents who are not routinely screened. An accurate and inexpensive carrier detection test is available (serum or leukocyte hexosaminidase A), and the disease can be reliably diagnosed by chorionic villus sampling in the 1st trimester of pregnancy in couples at risk (heterozygote parents).

Sandhoff disease is very similar to TSD in the mode of presentation, including progressive loss of motor and language milestones beginning at 6 mo of age. Seizures, cherry-red spots, macrocephaly, and doll-like facies are present in most patients; however, children with Sandhoff disease may also have splenomegaly. The visual evoked potentials (VEPs) are normal early in the course of Sandhoff disease and TSD, but become abnormal or absent as the disease progresses. The auditory brainstem responses show prolonged latencies. The diagnosis of Sandhoff disease is established by finding deficient levels of hexosaminidases A and B in serum and leukocytes. Children usually die by 3 yr of age. Sandhoff disease is caused by mutations in the HEXB gene located on chromosome 5q13.

Juvenile GM₃ gangliosidosis develops in mid-childhood, initially with clumsiness followed by ataxia. Signs of spasticity, athetosis, loss of language, and seizures gradually develop. Progressive visual loss is associated with optic atrophy, but cherry-red spots rarely occur in juvenile GM₃ gangliosidosis. A deficiency of hexosaminidase is variable (total deficiency to near normal) in these patients. Death occurs around 15 yr of age.

Adult GM₃ gangliosidosis is characterized by a myriad neurologic signs, including slowly progressive gait ataxia, spasticity, dystonia, proximal muscle atrophy, and dysarthria. Generally, visual acuity and intellectual function are unimpaired. Hexosaminidase A activity alone or hexosaminidases A and B activity is reduced significantly in the serum and leukocytes.

**Krabbe Disease (Globoid Cell Leukodystrophy)**

Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. The gene for KD (GALC) is located on chromosome 14q24.3-q24.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β-galactosidase. KD is a disorder of myelin destruction rather than abnormal myelin formation. Normally, myelinization begins in the 3rd trimester, corresponding with a rapid increase of galactocerebroside β-galactosidase activity in the brain. In patients with KD, galactocerebroside cannot be metabolized during the normal turnover of myelin because of deficiency of galactocerebrosideβ-galactosidase. When galactocerebroside is injected into the brains of experimental animals, a globoid cell reaction ensues. It is postulated that a similar phenomenon occurs in humans; nonmetabolized galactocerebroside stimulates the formation of globoid cells that reflect the destruction of oligodendrogial cells. Because oligodendroglial cells are responsible for the elaboration of myelin, their loss results in myelin breakdown, thus producing additional galactocerebroside and causing a vicious circle of myelin destruction.

The symptoms of KD become evident in the 1st few mo of life and include excessive irritability and crying, unexplained episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or milk allergy with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos and visual inattentiveness as a result of optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep-tendon reflexes, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 yr of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in KD. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms.

Late-onset KD has been described beginning in childhood or adolescence. Patients present with optic atrophy and cortical blindness, and their condition may be confused with adrenoleukodystrophy. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent. As with classic KD, globoid cells are abundant in the white matter, and leukocytes are deficient in galactocerebroside β-galactosidase. An examination of the cerebrospinal fluid shows an elevated protein content, and the nerve conduction velocities are markedly delayed as a result of segmental demyelination of the peripheral nerves. The VEPs decrease gradually in amplitude with no response in the late stages of the disease, and the auditory brainstem responses are characterized by the presence of only waves I and II. CT scans and MRI studies highlight the marked decrease in white matter, especially of the cerebellum and centrum semiovale, with sparing of the subcortical U fibers. Prenatal diagnosis is possible by the assay of galactocerebroside β-galactosidase activity in chorionic villi or in cultured amniotic fluid cells. Newborn screening may identify patients at risk for late-onset disease.
Metachromatic Leukodystrophy

This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity. The ARSA gene is located on chromosome 22q13-13qter. The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate within the myelin sheath of the central nervous system (CNS) and peripheral nervous system because of the inability to cleave sulfate from galactosyl-3-sulfate ceramide. The excessive cerebroside sulfate is thought to cause myelin breakdown and destruction of oligodendroglia. Prenatal diagnosis of metachromatic leukodystrophy (MLD) is made by assaying of arylsulfatase A activity in chorionic villi or cultured amniotic fluid cells. Cresyl violet applied to tissue specimens produces metachromatic staining of the sulfatide granules, giving the disease its name. Some individuals with low arylsulfatase A enzyme activity are clinically normal and have a pseudodeficiency state that can only be confirmed by additional genetic or biochemical tests. Those affected with MLD are generally classified according to age of onset: late infantile, juvenile, and adult.

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 yr of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required to walk. The extremities are hypotonic, and the deep-tendon reflexes are absent or diminished. Within the next several months, the child can no longer sit unsupported, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 yr from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired because of pseudobulbar palsies, and a feeding gastrostomy is required. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5-6 yr. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities and progressive changes in the VEPs, auditory brainstem responses, and somatosensory evoked potentials. CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebral white matter, and examination of the cerebrospinal fluid shows an elevated protein content. Bone marrow transplantation is a promising experimental therapy for the management of late infantile MLD, and early trials of enzyme replacement are being conducted. As with KD, favorable outcomes have been reported only in patients treated with less-severe disease or those identified very early in the course of the disease.

Juvenile MLD has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5-10 yr of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. Muscle tone becomes increased, and ataxia, dystonia, or tremor may be present. In the terminal stages, generalized tonic–clonic convulsions are prominent and are difficult to control. Patients rarely live beyond mid-adolescence.

Adult MLD occurs from the 2nd to 6th decade. Abnormalities in memory, psychomotor development, and personality changes are prominent features. Slowly progressive neurologic signs, including spasticity, dystonia, optic atrophy, and generalized convulsions, lead eventually to a bedridden state characterized by decorticate postures and unresponsiveness.

Bibliography is available at Expert Consult.

### 599.2 Neuronal Ceroid Lipofuscinoses

Jennifer M. Kwon

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal storage disorders characterized by visual loss, progressive dementia, seizures, motor deterioration, and early death. The NCLs are so named because of the intracellular accumulation of fluorescent lipopigments, ceroid and lipofuscin. They comprise a genetically and phenotypically heterogeneous group of disorders (currently there are at least 9 NCL types) that have traditionally been subclassified by age of onset, among other clinical features. They differ from one another in the associated ultrastructural patterns of the inclusions as seen by electron microscopy. Evaluation of neuronal biopsies (either brain, rectal, conjunctival, or skin) was once required for diagnosis. With the advent of enzymatic and molecular testing methods, clinicians can make specific NCL diagnoses using less-invasive methods (Table 599-2).

Infantile-type neuronal ceroid lipofuscinoses (INCL, Haltia-Santavuori) begins in the 1st yr of life with myoclonic seizures, intellectual deterioration, and blindness. Optic atrophy and brownish discoloration of the macula are evident on examination of the retina, and cerebellar ataxia is prominent. The electroretinogram typically shows small-amplitude or absent waveforms. Death occurs during childhood. The infantile form is caused by recessive mutations of the gene for the lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1) on chromosome 1p32. A number of cell types in INCL patients show characteristic intracellular fine granular osmiophilic deposits discernible by electron microscopy.

### Table 599-2 | Clinical and Genetic Characteristics of the Neuronal Ceroid Lipofuscinoses (NCL)

<table>
<thead>
<tr>
<th>NCL TYPE</th>
<th>GENE*</th>
<th>PROTEIN</th>
<th>AGE OF ONSET</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>CLN10</td>
<td>Cathepsin1</td>
<td>Birth (but can present later)</td>
<td>Severe seizures, blindness, rigidity, early death Can also present similar to late infantile forms</td>
</tr>
<tr>
<td>Infantile</td>
<td>CLN1</td>
<td>Palmitoyl-protein thioesterase-1 (PPT1)1</td>
<td>6-24 months</td>
<td>Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss Chronic course Initial visual loss followed then by slow mental and motor decline and seizures</td>
</tr>
<tr>
<td>Variant infantile</td>
<td>CLN1</td>
<td>Palmitoyl-protein thioesterase-1 (PPT1)1</td>
<td>3 yr to adulthood</td>
<td>Severe epilepsy, progressive with mental retardation</td>
</tr>
<tr>
<td>Late infantile</td>
<td>CLN2</td>
<td>Tripeptidyl peptidase-1 (TPP1)1</td>
<td>2-8 yr</td>
<td>Seizures, often severe and intractable; cognitive and motor decline; and visual loss</td>
</tr>
<tr>
<td></td>
<td>CLN5</td>
<td>Partially soluble protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLN6</td>
<td>Membrane protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLN7</td>
<td>Membrane protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLN8</td>
<td>Membrane protein</td>
<td>5-10 yr</td>
<td>Severe epilepsy, progressive with mental retardation Also have mental, motor disorder and seizures</td>
</tr>
<tr>
<td>Juvenile</td>
<td>CLN3</td>
<td>Membrane protein</td>
<td>4-10 yr</td>
<td>Visual loss is usually the initial presenting complaint Also have mental, motor disorder and seizures</td>
</tr>
</tbody>
</table>

*Note that all the NCL genes have the prefix CLN. The adult form (also called Kufs disease, with locus CLN4, caused by mutations in DNAJC5) is not well characterized and is not included in the table.

1Direct genetic testing is available for all.

2Enzyme testing available.
Bibliography


A subset of children with PPT1 enzyme deficiency has a much less-severe course with clinical features resembling those of the juvenile-onset NCL patients. Clinically, these variant INCL patients have a course that is often quite distinct from the typical,classic rapidly degenerating infantile form. Yet they have PPT1 deficiency and granular osmiophilic deposits on pathology. There is no clear CLN1 genotype that predicts severity of phenotype.

Late infantile-type neuronal ceroid lipofuscinose (LINCL, Jansky-Bielschowsky) generally presents with myoclonic seizures beginning between 2 and 4 yr of age in a previously normal child. Dementia and ataxia are combined with a progressive loss of visual acuity and microcephaly. Examination of the retina shows marked attenuation of vessels, peripheral black bone spicule pigmentary abnormalities, optic atrophy, and a subtle brown pigment in the macular region. The electroretinogram and VEP are abnormal early in the course of disease. The autofluorescent material is deposited in neurons, fibroblasts, and secretory cells. Electron microscopic examination of the storage material in skin or conjunctival biopsy material typically shows curvilinear profiles. LINCL can be caused by autosomal recessive mutations of several different genes: CLN2 gene, which codes for a tripeptidyl peptidase-1 (TPP1) that is essential for the degradation of cholecystokinin-8, as well as the CLN5, CLN6, and CLN8 genes that code for membrane proteins that have not been completely characterized. CLN8 is also known as the locus of Northern epilepsy syndrome, which is often called progressive epilepsy with mental retardation.

Juvenile type neuronal ceroid lipofuscinose (JNCL, Spielmeyer-Vogt or Batten disease) is the most common form of NCL disease and is generally caused by autosomal-recessive mutations in CLN3. (Patients who present clinically with JNCL but have PPT1 or TPP1 deficiency are said to have variant INCL or LINCL, respectively.) Children affected with JNCL tend to develop normally for the 1st 5 yr of life. Their initial symptom is usually progressive visual loss and their retinal pigmentary changes often results in an initial diagnosis of retinitis pigmentosa. The fundoscopic changes are similar to those for the late infantile type. After disease onset, there may be rapid decline with changes in cognition and personality, motor incoordination, and seizures. Myoclonic seizures are not as prominent as in LINCL, but parkinsonism can develop and impair ambulation. Patients die in their late twenties to early thirties. In JNCL caused by CLN3, the electron microscopy of tissues show deposits called fingerprint profiles, and routine light microscopy of a peripheral blood smear may show lymphocyte vacuoles.

Bibliography is available at Expert Consult.

599.3 Adrenoleukodystrophy
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See Chapter 86.2.

599.4 Sialidosis
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Sialidosis is the result of lysosomal sialidase deficiency, secondary to autosomal recessive mutations in the sialidase (α-neuraminidase, NEU1) gene on chromosome 6p21.3. The accumulation of sialic acid–containing oligosaccharides with markedly increased urinary excretion of sialic acid–containing oligosaccharides is associated with clinical presentations that range from the milder sialidosis type I to the more severe sialidosis type II associated with both neurologic and somatic features.

Sialidosis type I, the cherry-red spot myoclonus syndrome, usually presents in the 2nd decade of life, when a patient complains of visual deterioration. Inspection of the retina shows a cherry-red spot, but, unlike patients with TSD, visual acuity declines slowly in individuals with cherry-red spot myoclonus syndrome. Myoclonus of the extremities is gradually progressive and often debilitating and eventually renders patients nonambulatory. The myoclonus is triggered by voluntary movement, touch, and sound and is not controlled with anticonvulsants. Generalized convulsions responsive to antiepileptic drugs occur in most patients.

Sialidosis type II patients present at a younger age and have cherry-red spots and myoclonus, as well as somatic involvement, including coarse facial features, corneal clouding (rarely), and dysostosis multiplex, producing anterior beaking of the lumbar vertebrae. Type II patients may be further subclassified into congenital and infantile (childhood) forms, depending on the age at presentation. Examination of lymphocytes shows vacuoles in the cytoplasm, biopsy of the liver demonstrates cytoplasmic vacuoles in Kupffer cells, and membrane-bound vacuoles are found in Schwann cell cytoplasm, all attesting to the multigorgan nature of sialidosis type II. No distinctive neuroimaging findings or abnormalities in electrophysiologic studies are noted in this group of disorders. Patients with sialidosis have been reported to live beyond the 5th decade.

Some cases of what appears to be sialidosis type II are the result of combined deficiencies of β-galactosidase and α-neuraminidase resulting from deficiency of protective protein/cathepsin A that prevents premature intracellular degradation of these 2 enzymes. These patients have galactosialidosis and they are clinically indistinguishable from those with sialidosis type II. Consequently, patients who have features of sialidosis type II with marked urinary excretion of oligosaccharides should be tested for protective protein/cathepsin A deficiency as well as sialidase deficiency.

Bibliography is available at Expert Consult.

599.5 Miscellaneous Disorders
Jennifer M. Kwon

PELIZAEUS-MERZBACHER DISEASE
Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder characterized by nystagmus and abnormalities of myelin. PMD is caused by mutations in the proteolipid protein (PLP1) gene, on chromosome Xq22, which is essential for CNS myelin formation and oligodendrocyte differentiation. Mutations in the same gene can cause familial spastic paraparesis (progressive spastic paraparesis type 2, SPG2). PLP1 mutations causing disease include point mutations, deletions, gene duplications, and other gene dosage changes.

Classically, classic PMD is recognized by nystagmus and roving eye movements with head nodding during infancy. Developmental milestones are delayed; ataxia, choreoathetosis, and spasticity ultimately develop. Optic atrophy and dysarthria are associated findings, and death occurs in the 2nd or 3rd decade. The major pathologic finding is a loss of myelin with intact axons, suggesting a defect in the function of oligodendroglia. An MRI scan shows a symmetric pattern of delayed myelination. Multimodal-evoked potential studies demonstrate early in the course a pattern consisting of loss of waves III-V on the auditory brainstem response. This finding is useful in the investigation of nystagmus in infant boys. VEPs show prolonged latencies, and somatosensory evoked potentials show absent cortical responses or delayed latencies. It is now recognized that a broad spectrum of phenotypes, including SPG2 and peripheral nerve abnormalities, can also result from mutations in the PLP1 gene.

There is a PMD-like syndrome caused by autosomal recessive mutations in the gap junction protein alpha 12 (GJA12, or connexin 47). Individuals with GJA12 mutations have a clinical and radiologic phenotype like PMD including hypomyelinating leukodystrophy.

ALEXANDER DISEASE
This is a rare disorder that causes progressive macrocephaly and leukodystrophy. Alexander disease is caused by dominant mutations in the glial fibrillary acidic protein (GFAP) gene, on chromosome 17q21
Bibliography
Bibliography

and cases are usually sporadic in their families. Pathologic examination of the brain discloses deposition of eosinophilic hyaline bodies called Rosenthal fibers in astrocyte processes. These accumulate in a perivascular distribution throughout the brain. In the classic infantile form of Alexander disease, degeneration of white matter is most prominent frontally. Diagnosis may be suggested by MRI (Fig. 599-3) and MR spectroscopy demonstrating abnormal metabolic substrates. Affected children develop progressive loss of intellect, spasticity, and unresponsive seizures causing death by 5 yr of age. However, there are milder forms that present later in life and that may not have the characteristic frontal predominance or megalencephaly.

**CANAVAN SPONGY DEGENERATION**
See Chapter 85.15.

**OTHER LEUKODYSTROPHIES**
Metabolic and degenerative disorders can present with significant cerebrocortical white matter changes, such as some mitochondrial disorders (see Chapters 86.1 and 598.2) and glutaric aciduria type 1 (see Chapter 85.14). In addition, the broader use of MRI has brought to light new leukodystrophies. One example is vanishing white matter disease or childhood ataxia with CNS hypomyelination characterized by ataxia and spasticity. Some patients also have optic atrophy, seizures, and cognitive deterioration. The age of presentation and the rapidity of decline can be quite variable. In the early-onset forms, decline is usually rapid and followed quickly by death; in the later-onset forms, mental decline is usually slower and milder. Interestingly, acute demyelination in these disorders can be triggered by fever or fright. The diagnosis of vanishing white matter disease or childhood ataxia with CNS hypomyelination is based on clinical findings, characteristic abnormalities on cranial MRI, and autosomal recessive mutations in 1 of 5 causative genes (EIF2B1, EIF2B2, EIF2B3, EIF2B4, and EIF2B5) encoding the 5 subunits of the eucaryotic translation initiation factor, eIF2B.

**MENKES DISEASE**
Menkes disease (kinky hair disease) is a progressive neurodegenerative condition inherited as a X-linked recessive trait. The Menkes gene codes for a copper-transporting, P-type adenosine triphosphatase, and mutations in the protein are associated with low serum copper and ceruloplasmin levels, as well as a defect in intestinal copper absorption and transport. Symptoms begin in the 1st few mo of life and include hypothermia, hypotonia, and generalized myoclonic seizures. The facies are distinctive, with chubby, rosy cheeks and kinky, colorless, friable hair. Microscopic examination of the hair shows several abnormalities, including trichorrhexis nodosa (fractures along the hair shaft) and pili torti (twisted hair). Feeding difficulties are prominent and lead to failure to thrive. Severe mental retardation and optic atrophy are constant features of the disease. Neuropathologic changes include tortuous degeneration of the gray matter and marked changes in the cerebellum with loss of the internal granule cell layer and necrosis of the Purkinje cells. Death occurs by 3 yr of age in untreated patients.

Copper-histidine therapy may be effective in preventing neurologic deterioration in some patients with Menkes disease, particularly when treatment is begun in the neonatal period or, preferably, with the fetus. These presymptomatic children are currently identified because of a family history of an affected brother. Copper is essential in the early stages of CNS development, and its absence probably accounts for the neuropathologic changes. Infants diagnosed presymptomatically in the 1st 10 days of life can be started on an experimental protocol of daily copper-histidine subcutaneous injections (as of 2015, only available at NIH under a program supervised by Dr. Stephen Kaler). Optimal response to copper-histidine injection treatment appears to occur only in patients who are identified in the newborn period and whose mutations permit residual copper-transport activity.

The **occipital horn syndrome**, a skeletal dysplasia caused by different mutations in the same gene as that involved in Menkes disease, is a relatively mild disease. The 2 diseases are often confused, because the biochemical abnormalities are identical. Resolution of the uncertainty about treatment of patients with Menkes disease will require careful genotype-phenotype correlation, along with further clinical trials of copper therapy.

**RET SYNDROME**
This syndrome is not strictly speaking a degenerative disease, but a disorder of early brain development marked by a period of developmental regression and deceleration of brain growth after a relatively
normal neonatal course. It occurs predominantly in girls. The frequency is approximately 1 in 15,000-22,000 children. Rett syndrome is caused by mutations in MeCP2, a transcription factor that binds to methylated CpG islands and silences transcription. Development may proceed normally until 1 yr of age, when regression of language and motor milestones and acquired microcephaly become apparent. An ataxic gait or fine tremor of hand movements is an early neurologic finding. Most children develop peculiar sighing respirations with intermittent periods of apnea that may be associated with cyanosis. The hallmark of Rett syndrome is repetitive hand-wringing movements and a loss of purposeful and spontaneous use of the hands; these features may not appear until 2-3 yr of age. Autistic behavior is a typical finding in all patients. Generalized tonic-clonic convulsions occur in the majority and are usually well controlled by anticonvulsants. Feeding disorders and poor weight gain are common. After the initial period of neurologic regression, the disease process appears to plateau, with persistence of the autistic behavior. Cardiac arrhythmias may result in sudden, unexpected death at a rate that is higher than the general population. Generally girls survive into adulthood.

Postmortem studies show significantly reduced brain weight (60-80% of normal) with a decrease in the number of synapses, associated with a decrease in dendritic length and branching. The phenotype may be related to failure to suppress expression of genes that are normally silent in the early phases of postnatal development. Although very few males survive with the classic Rett syndrome phenotype, genotyping of boys without the classic Rett syndrome phenotype but with intellectual disability and other atypical neurologic features has detected a significant number with mutations in MeCP2. Mutations in MeCP2 have been demonstrated in normal female carriers, females with Angelman syndrome, and in males with fatal encephalopathy, Klinefelter (47 XXY) syndrome, and familial X-linked mental retardation.

Some girls have an atypical Rett phenotype associated with severe myoclonic seizures in infancy, slowing of head growth, and developmental arrest and have mutations in another X-linked gene encoding for cyclin-dependent kinase–like 5 (CDKL5), which may interact with MeCP2 and other proteins regulating gene expression.

**SUBACUTE SCLerosING PANECEPHALITIS**

This is a rare, progressive neurologic disorder caused by persistent measles virus infection of the CNS (see Chapter 246). The number of reported cases has decreased dramatically to 0.06 cases/million population, paralleling the decline in reported measles cases. The initial clinical manifestations include personality changes, aggressive behavior, and impaired cognitive function in individuals who have been exposed to natural measles virus in early childhood. Myoclonic seizures soon dominate the clinical picture. Later, generalized tonic-clonic convulsions, hypertonia, and choreoathetosis become evident, followed by progressive bulbar palsy, hyperthermia, and decerebrate postures. Funduscopic examination early in the course of the disease reveals papilledema in approximately 20% of the cases. Optic atrophy, chorioretinitis, and macular pigmentation are observed in most patients. The diagnosis is established by the typical clinical course and 1 of the following: (1) measles antibody detected in the cerebrospinal fluid, (2) a characteristic electroencephalogram consisting of bursts of high-voltage slow waves interspersed with a normal background that occur with a constant periodicity in the early stages of the disease, and (3) typical histologic findings in the brain biopsy or postmortem specimen. Treatment with a series of antiviral agents has been attempted without success. Death occurs usually within 1-2 yr from the onset of symptoms.

**NEURODEGENERATION WITH BRAIN IRON ACCUMULATION**

Neurodegeneration with brain iron accumulation represents multiple, age-of-onset-dependent disorders characterized by extrapyramidal symptoms, intellectual deterioration and regression, with iron deposition in the basal ganglia. There is significant phenotype variability of these disorders; however, a characteristic finding on MRI demonstrates symmetric T2 signal homogeneous hypointensity. Common neurodegeneration with brain iron accumulation disorders are distinguished in Table 599-3 and an approach to their diagnosis is noted in Figure 599-4. Clinical features, which are highly variable, may include dystonia, parkinsonism, ataxia, spasticity, psychiatric symptoms, and intellectual impairment. Treatment should focus on the specific disorder and is usually symptomatic relief rather than curative. Iron chelation has been attempted without major long-term benefit.

*Bibliography is available at Expert Consult.*

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**Figure 599-4** Clinical and radiographic approach to neurodegeneration with brain iron accumulation. NBIA, neurodegeneration with brain iron accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood. (From Kruer MC, Boddaert N: Neurodegeneration with brain iron accumulation: a diagnostic algorithm. Semin Pediatr Neurol 19:67–74, 2012, Fig. 1.)
Bibliography
Table 599-3: Overview of Neurodegeneration with Brain Iron Accumulation Conditions and Genes (if Known)

<table>
<thead>
<tr>
<th>CONDITION (ACRONYM)</th>
<th>SYNONYM</th>
<th>GENE</th>
<th>CHROMOSOMAL POSITION</th>
<th>LB PATHOLOGY</th>
<th>AGE OF ONSET</th>
<th>CLINICAL PRESENTATION</th>
<th>AGE OF ONSET</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKAN</td>
<td>NBIA1</td>
<td>PANK2</td>
<td>20p13</td>
<td>No</td>
<td>Early childhood, around age 3</td>
<td>Typical PKAN</td>
<td>Teens or early adulthood</td>
<td>Atypical PKAN</td>
</tr>
<tr>
<td>PLAN</td>
<td>NBIA2, PARK14</td>
<td>PLA2G6</td>
<td>22q12</td>
<td>√</td>
<td>Infancy</td>
<td>Infantile neuroaxonal dystrophy</td>
<td>Teens or early adulthood</td>
<td>Dystonia parkinsonism</td>
</tr>
<tr>
<td>FAHN</td>
<td>SPG35</td>
<td>FA2H</td>
<td>16q23</td>
<td>Not known</td>
<td>Childhood</td>
<td>Leukodystrophy, hereditary spastic paraplegia</td>
<td>Adulthood (age range up to 30 yr)</td>
<td>May resemble idiopathic PD</td>
</tr>
<tr>
<td>MPAN</td>
<td>—</td>
<td>C19orf12</td>
<td>19q12</td>
<td>√</td>
<td>Pyramidal extrapyramidal syndrome</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Kufor-Rakeb disease</td>
<td>PARK9</td>
<td>ATP13A2</td>
<td>1p36</td>
<td>√</td>
<td>Childhood-teens</td>
<td>Parkinsonism, pyramidal tract signs, eye movement disorder</td>
<td>Then: 20s to 30s</td>
<td>Sudden onset progressive dystonia parkinsonism</td>
</tr>
<tr>
<td>BPAN</td>
<td>SENDA syndrome</td>
<td>WDR45</td>
<td>Xp11.23</td>
<td>Not known</td>
<td>Childhood</td>
<td>Encephalopathy with psychomotor regression, then static</td>
<td>Then: 20s to 30s</td>
<td>Sudden onset progressive dystonia parkinsonism</td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td>—</td>
<td>CP</td>
<td>3q23</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>50s (range: 16-70)</td>
<td>Extrapliald, diabetes, dementia</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>—</td>
<td>FTL</td>
<td>19q13</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>40s</td>
<td>Chorea, dystonia, dementia</td>
</tr>
<tr>
<td>Idiopathic late-onset cases</td>
<td>—</td>
<td>Probably heterogeneous</td>
<td>Probably heterogeneous</td>
<td>Heterogeneous</td>
<td>—</td>
<td>—</td>
<td>Heterogeneous</td>
<td>Parkinsonism, in may resemble idiopathic PD</td>
</tr>
</tbody>
</table>

√ Present; BPAN, beta-propeller associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FAHN, fatty acid 2-hydroxylase-associated neurodegeneration; FTL, ferritin light chain; MPAN, mitochondrial membrane-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PD, Parkinson disease; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, PLA2G6-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia.

From Schneider SA, Zara G, Nardocci N: Pathophysiology and treatment of neurodegeneration with brain iron accumulation in the pediatric population, Curr Treat Option Neurol 15:652-667, 2013, Table 1.
Acquired demyelinating disorders of the central nervous system (CNS) result in neurologic dysfunction caused by immune-mediated attacks on white matter insulating the brain, optic nerves and spinal cord. The white matter is insulted by myelin contained within oligodendrocytes wrapping around nerve axons. In contrast to genetically determined leukodystrophies (sometimes called dysmyelinating disorders) that produce disrupted white matter, acquired demyelinating disorders generally target normally formed white matter. Pediatric demyelinating syndromes are characterized clinically by (1) localization of neurologic deficits (i.e., single site, such as spinal cord [transverse myelitis], optic nerves [optic neuritis] or brainstem, vs polyregional demyelination); (2) the presence vs absence of encephalopathy; and (3) disease course (i.e., monophasic vs repeated attacks involving either the same or new CNS regions). Major demyelinating disorders in childhood include acute disseminated encephalomyelitis (ADEM), typically a self-limited disorder, and relapsing–remitting multiple sclerosis (MS). MRI of brain and spine is useful to initially characterize symptomatic and clinically silent demyelinating lesions, but serial MRI is often required to distinguish self-limited vs chronic demyelinating syndromes, especially in the youngest child. Additional studies, such as cerebrospinal fluid (CSF) analysis, autoimmune and genetic testing, and sometimes even brain biopsy, may be required to evaluate for mimickers of demyelination, such as neoplasm, infection, systemic rheumatologic disorders, isolated CNS angitis, mitochondrial disease, and leukodystrophies (Tables 600-1 and 600-2).

**600.1 Multiple Sclerosis**

Pediatric MS is a chronic demyelinating disorder of the brain, spinal cord, and optic nerves characterized by a relapsing–remitting course of neurologic events without encephalopathy separated in time and space.

**Epidemiology**

Pediatric MS is rare, with an estimated 2–5% of MS patients experiencing their first symptoms before age 18 yr. Pediatric MS has a slight male predominance when disease onset is before age 6 yr, but by age 12 yr, females outnumber males 2:1.

**Pathogenesis**

A complex interplay of environmental, infectious, and genetic factors influence MS susceptibility. Immune system dysregulation involving T and B lymphocytes triggers inflammation, axonal demyelination, axonal loss, and regeneration within both white and gray matter. Inflammatory infiltrates within actively demyelinating lesions of relapsing–remitting MS are targets for disease modifying agents (DMAs). Neurodegenerative changes predominate in progressive forms of MS.

**Clinical Manifestations**

Presenting symptoms in pediatric MS include hemiparesis or paraparesis; unilateral or, less often, bilateral optic neuritis; focal sensory loss; ataxia; diplopia; dysarthria; or bowel/bladder dysfunction (Table 600-3). Polyregional symptoms are reported in 30% of patients. Encephalopathy is less common and suggests consideration of ADEM or possibly neuromyelitis optica (NMO).

**Laboratory Findings**

Cranial MRI exhibits discrete T2 lesions in cerebral white matter, particularly periventricular regions as well as brainstem, cerebellum, and juxtacortical and deep gray matter. Alternatively, large tumefactive T2 lesions may be seen. Spine MRI typically shows partial-width cord lesions restricted to 1-2 spine segments. CSF may be normal or exhibit mild pleocytosis, particularly in younger children. Abnormal MS profile (increased immunoglobulin [lg] G index, and/or CSF oligoclonal bands) increase likelihood of MS but may be negative in 10–60% of pediatric MS patients, particularly prepubertal children; they also may be occasionally positive in ADEM or autoimmune encephalitis (Fig. 600-1). Abnormal evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways.

**Diagnosis and Differential Diagnosis**

Pediatric MS can usually be diagnosed following 2 demyelinating episodes without encephalopathy localizing to distinct CNS regions, lasting longer than 24 hr and separated by more than 30 days, provided no other plausible explanation exists. Current MS diagnostic criteria use MRI to serve as a surrogate for recurrent demyelination, enabling MS diagnosis after the first event. For adults and children >12 yr, the initial MRI may be sufficient to diagnose MS if it demonstrates dissemination in space (≥2 T2 lesions involving juxtacortical, periventricular, infratentorial, or spine regions) and time (presence of asymptomatic gadolinium-enhancing lesion and nonenhancing T2 lesion in same scan). Alternatively, MS can be diagnosed with a follow-up MRI at any time interval exhibiting accumulation of T2 or gadolinium-enhancing lesions in the brain or spine. Challenges arise in distinguishing pediatric MS from other acquired demyelinating disorders.
### Table 600-2 | IPMSSG 2012 Definitions for Pediatric Acute Demyelinating Disorders of the Central Nervous System

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>IPMSSG 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>- A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, unless caused by fever</td>
</tr>
<tr>
<td>Monophasic ADEM</td>
<td>- A first polyfocal clinical CNS event with presumed inflammatory cause</td>
</tr>
<tr>
<td></td>
<td>- Encephalopathy that cannot be explained by fever is present</td>
</tr>
<tr>
<td></td>
<td>- MRI typically shows diffuse, poorly demarcated, large, &gt;1-2 cm lesions involving predominantly the cerebral white matter; T1 hypointense white matter lesions are rare; deep gray-matter lesions (e.g., thalamus or basal ganglia) can be present</td>
</tr>
<tr>
<td></td>
<td>- No new symptoms, signs or MRI findings after 3 mo of the incident ADEM</td>
</tr>
<tr>
<td>Recurrent ADEM</td>
<td>- See multiphasic ADEM</td>
</tr>
<tr>
<td>Multiphasic ADEM</td>
<td>- New event of ADEM 3 mo or more after the initial event that can be associated with new or reemergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent</td>
</tr>
<tr>
<td>MS</td>
<td>- Any of the following:</td>
</tr>
<tr>
<td></td>
<td>- Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than 1 area of the CNS</td>
</tr>
<tr>
<td></td>
<td>- Single clinical event and MRI features rely on 2010 Revised McDonald criteria for DIS and DIT (but criteria relative for DIT for a single attack and single MRI only apply to children ages 2-12 yr and only apply to cases without an ADEM onset)</td>
</tr>
<tr>
<td>NMO</td>
<td>- All are required:</td>
</tr>
<tr>
<td></td>
<td>- Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>- Acute myelitis</td>
</tr>
<tr>
<td></td>
<td>- At least 2 of 3 supportive criteria</td>
</tr>
<tr>
<td></td>
<td>- Contiguous spinal cord MRI lesion S3 vertebral segments</td>
</tr>
<tr>
<td></td>
<td>- Brain MRI not meeting diagnostic criteria for MS</td>
</tr>
<tr>
<td></td>
<td>- Anti–aquaporin-4 immunoglobulin G–seropositive status</td>
</tr>
<tr>
<td></td>
<td>- ADEM followed 3 mo later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS</td>
</tr>
</tbody>
</table>

The 2001 McDonald MRI criteria for DIS require 3 of the following 4 MRI features: 29 T2 lesions or 1 gadolinium-enhancing lesion; 23 periventricular lesions; 21 infratentorial lesion(s); 21 juxtacortical lesion(s). The DIT criteria require subsequent white-matter lesions whose timing depends on the temporal relation of the initial MRI with the onset of the clinical symptoms.

The 2010 Revised McDonald MRI criteria for DIS require the presence of at least 2 of the following 4 criteria: 21 lesions in each of the 4 locations; periventricular, juxtacortical, infratentorial, and spinal cord. The 2010 Revised McDonald MRI criteria for DIT can be satisfied either by the emergence of newT2 lesions (with or without enhancement) on serial scan(s) or can be met on a single baseline scan if there exists simultaneous presence of a clinically silent gadolinium-enhancing lesion and a nonenhancing lesion.

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; IPMSSG, International Pediatric Multiple Sclerosis Study Group; MS, multiple sclerosis; NMO, neuromyelitis optica.


### Table 600-3 | Symptoms and Signs of Multiple Sclerosis by Site

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Deficits in attention, reasoning, and executive function (early); dementia (late)</td>
</tr>
<tr>
<td></td>
<td>Upper motor neuron signs</td>
</tr>
<tr>
<td></td>
<td>Hemisensory and motor</td>
</tr>
<tr>
<td></td>
<td>Affective (mainly depression)</td>
</tr>
<tr>
<td></td>
<td>Epilepsy (rare)</td>
</tr>
<tr>
<td></td>
<td>Focal cortical deficits (rare)</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Unilateral painful loss of vision</td>
</tr>
<tr>
<td></td>
<td>Scotoma, reduced visual acuity, color vision, and relative afferent papillary defect</td>
</tr>
<tr>
<td>Cerebellum and cerebellar pathways</td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Postural and action tremor, dysarthria</td>
</tr>
<tr>
<td></td>
<td>Limb incoordination and gait ataxia</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Diplopia, oscillopsia</td>
</tr>
<tr>
<td></td>
<td>Nystagmus, internuclear and other complex ophthalmoplegias</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
</tr>
<tr>
<td></td>
<td>Pseudobulbar palsy</td>
</tr>
<tr>
<td></td>
<td>Impaired swallowing</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal symptoms</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Upper motor neuron signs</td>
</tr>
<tr>
<td></td>
<td>Spasticity</td>
</tr>
<tr>
<td></td>
<td>Stiffness and painful spasms</td>
</tr>
<tr>
<td></td>
<td>Bladder dysfunction</td>
</tr>
<tr>
<td></td>
<td>Erectile impotence</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>Other</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Temperature sensitivity and exercise intolerance</td>
</tr>
</tbody>
</table>

Treatment

Relapses causing functional disability may be treated with methylprednisolone, 20-30 mg/kg/day (max: 1,000 mg/day) for 3-5 days, with or without prednisone taper. DMAs reduce relapse frequency and T2 lesion load, mainly by targeting the inflammatory response that predominates during the relapsing-remitting phase of MS (Table 600-6). There are 4 injectable DMAs, 3 oral DMAs, and 2 infused DMAs approved by the FDA for adult MS, but to date, none of these agents has a pediatric MS indication. Injectable agents, first approved in the mid-1990s (interferon-beta1α SC or IM or interferon-beta1β SC; glatiramer acetate SC) have some side effects such as flu-like side effects and risk of transaminase elevation with interferon-beta or requirement for daily injections with glatiramer acetate but otherwise have an excellent safety record so are still recommended as first-line therapy in pediatric MS. There are 4 injectable DMAs, 3 oral DMAs, and 2 infused DMAs approved by the FDA for adult MS, but to date, none of these agents has a pediatric MS indication. Injectable agents, first approved in the mid-1990s (interferon-beta1α SC or IM or interferon-beta1β SC; glatiramer acetate SC) have some side effects such as flu-like side effects and risk of transaminase elevation with interferon-beta or requirement for daily injections with glatiramer acetate but otherwise have an excellent safety record so are still recommended as first-line therapy in pediatric MS. Three oral DMAs (fingolimod, teriflunomide, dimethyl fumarate) have been FDA-approved since 2010, but despite ease of oral administration, enthusiasm is tempered by reports of severe side effects or even death from reactivation of latent viruses (fingolimod, dimethyl fumarate) and potential of severe birth defects (teriflunomide). Intravenous DMAs (natalizumab, mitoxantrone) are second-line agents.

**Figure 600-1 Criteria for the diagnosis of multiple sclerosis.** The principle is to establish dissemination in time and place of lesions, meaning that episodes affecting separate sites within the central nervous system have occurred at least 30 days apart. MRI can substitute for 1 of these clinical episodes. Dissemination in time of magnetic resonance lesions requires simultaneous presence of asymptomatic gadolinium-enhancing and asymptomatic lesions or followup MRI showing accumulation of a new gadolinium-enhancing lesion or T2 lesion. Criteria for MRI definition of dissemination in space require 2 or more lesions in periventricular, juxtacortical, or infratentorial regions or spine. Primary progressive MS is very rare in childhood but can be diagnosed after 1 yr of a progressive deficit and 2 of the following: (1) a positive brain MRI; (2) a positive spinal cord MRI; and (3) positive oligoclonal bands. Patients having an appropriate clinical presentation but who do not meet all of the diagnostic criteria can be classified as having possible MS. CSF, cerebrospinal fluid. (From Compston A, Coles A: Multiple sclerosis, Lancet 372:1502–1517, 2008, Fig. 1.)
used only after failure of first-line injectable or oral agents. Natalizumab therapy is associated with the risk of developing progressive multifocal encephalopathy (CNS infection with human polyomavirus JC). Mitoxantrone has a lifetime dose limit because of cardiotoxicity and is associated with subsequent development of acute myelogenous lymphoma in 2 of 802 MS patients (0.25%).

**PROGNOSIS**

Retrospective studies of patients diagnosed with MS prior to widespread dimethyltryptamine use suggest slower disease progression in pediatric MS patients compared to adults. Despite a longer time to irreversible disability (20-30 yr), pediatric MS patients acquire irreversible disability at a younger age than adults.

Bibliography is available at Expert Consult.

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**Table 600-4: Clinical Features That May Distinguish ADEM from First Attack of MS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>ADEM</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;10 yr</td>
<td>&gt;10 yr</td>
</tr>
<tr>
<td>Stupor/coma</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Fever/vomiting</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Family history</td>
<td>No</td>
<td>20%</td>
</tr>
<tr>
<td>Sensory complaints</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Bilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Manifestations</td>
<td>Polysymptomatic</td>
<td>Monosymptomatic</td>
</tr>
<tr>
<td>CSF</td>
<td>Pleocytosis (lymphocytosis)</td>
<td>Oligoclonal bands</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Follow-up</td>
<td>No new lesions</td>
<td>New lesions</td>
</tr>
</tbody>
</table>

Some features that may help distinguish an initial acute episode of demyelination from a first attack of MS in children. Final diagnosis of MS is based on follow-up evaluation and possibly MRI.

+ More likely to be present; −, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis.

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**Table 600-5: MRI Characteristics for Dissemination in Space That Increase the Likelihood of a Pediatric Multiple Sclerosis Diagnosis**

<table>
<thead>
<tr>
<th>Barkhof (KIDMUS)†</th>
<th>Mikaeloff (Diagnosis MS)§</th>
<th>Callen (Diagnostic MS)¶</th>
<th>Callen (Diagnostic MS)§</th>
<th>Verhey (Differential)‖</th>
<th>Polman (2010 Revised McDonald Criteria)¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 of 4: ≥2 T2 lesions or 1 gadolinium enhancing ≥3 Periventricular ≥1 Infratentorial ≥1 Juxtacortical</td>
<td>1 of 2: Lesions perpendicular to long axis of corpus callosum</td>
<td>2 of 3: Absence of a diffuse bilateral lesion pattern</td>
<td>2 of 3: ≥2 Lesions on T2-weighted images 2 Periventricular lesions ≥1 Brainstem lesions</td>
<td>2 of 2: ≥2 Periventricular lesions ≥1 Hypointense lesions on T1 images</td>
<td>2 of 4: ≥1 Periventricular ≥1 Juxtacortical ≥1 Infratentorial ≥1 Spinal cord</td>
</tr>
</tbody>
</table>

---

**600.2 Neuromyelitis Optica**

Jayne M. Ness

NMO (Devic disease) is a demyelinating disorder characterized by monophasic or polyphasic episodes of optic neuritis and/or transverse myelitis. It was once thought that NMO was a variant of MS; but identification of the NMO antibody against the aquaporin-4 water channel has broadened the spectrum of NMO to include brainstem syndromes and recurrent forms of optic neuritis and transverse myelitis (see Table 600-2). NMO spectrum disorder frequently involves symptomatic or silent MRI lesions demonstrating demyelination of the cerebral cortex and other regions of the brain.

**EPIDEMIOLOGY**

NMO has an age of onset of 31.2 ± 11 yr. In 1 study, in monophasic patients, the range of age of onset was 1-54 yr; in polyphasic patients, the range was 6-72 yr. NMO is more common in females than in males; 65% of monophasic and 80-85% of polyphasic NMO patients are female. It is also more common in Asians than in blacks or whites and appears to have a higher mortality rate in individuals of African descent than in others.

**PATHOGENESIS**

NMO is associated with IgG antibodies against the aquaporin-4 water channel, which is most abundant on astrocyte foot processes within periventricular regions, brainstem, optic nerves, and spinal cord. Antibody binding to aquaporin-4 activates the classical complement pathway with Csβ-C9 components leading to leukocytes attraction and degranulation, causing astrocyte death. Chemokines from dying astrocytes and activated leukocytes attract macrophages, leading to death of oligodendrocytes and neurons with subsequent necrosis or even cavitation in affected tissues. Although most cases of NMO are idiopathic and only occasional familial cases have been reported, there have been reports of postinfectious NMO. HIV, syphilis, chlamydia, varicella, cytomegalovirus, and Epstein-Barr virus are associated with subsequent development of NMO. Aquaporin-4 antibody–positive NMO may follow or occur simultaneously with N-methyl-D-aspartate receptor antibody autoimmune encephalitis.

**CLINICAL MANIFESTATIONS**

NMO presents with optic neuritis or transverse myelitis or brainstem symptoms such as intractable vomiting or hiccups, diplopia, facial
Bibliography
weakness or numbness or dysphagia. Optic neuritis or transverse myelitis may occur simultaneously or may be separated in time by weeks or even years. Some present with an encephalopathy mimicking ADEM. Others exhibit endocrinopathies such as the syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus, or disrupted puberty. The symptoms and signs of transverse myelitis depend on the spinal level and completeness of the inflammatory changes. NMO differs from MS in that recovery of visual and spinal cord function is generally not as complete after each episode; optic neuritis is more frequently bilateral in NMO than in MS.

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**Table 600-6 Overview of Available and Emerging Therapies in Pediatric Multiple Sclerosis**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>MEDICATION CLASS</th>
<th>MECHANISM IN MS</th>
<th>SIDE EFFECTS</th>
<th>STUDIES DESCRIBING DRUG EFFICACY IN PEDIATRIC MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE THERAPIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α or β</td>
<td>Immunomodulator</td>
<td>Modulates T cells and cytokine production</td>
<td>Flu-like symptoms; transaminitis; leukopenia; tissue necrosis at injection site (rare)</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Immunomodulator</td>
<td>Modulates T cells and reduces antigen presentation</td>
<td>Flushing, lipodystrophy at injection sites</td>
<td>Prospective single center</td>
</tr>
<tr>
<td><strong>SECOND-LINE THERAPIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab†</td>
<td>Monoclonal antibody</td>
<td>Targets α-integrin; prevents T-cell migration into CNS and other tissues</td>
<td>Overall PML rate ~1 in 500 patients, but lower in subgroups; immune reconstitution syndrome after discontinuation; melanoma; infusion reaction; transaminitis (rare)</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Chemotherapeutic</td>
<td>DNA alklylation; effects include cytotoxic immune cell depletion</td>
<td>Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Mitoxantrone*</td>
<td>Chemotherapeutic</td>
<td>Disrupts DNA synthesis; effects include cytotoxic immune cell depletion</td>
<td>Significant long-term safety risks, including cardiotoxicity (1 in 200 patients) and secondary leukemia (1 in 125 patients); opportunistic infections</td>
<td>Retrospective single center</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Monoclonal antibody</td>
<td>Targets/inaactivates interleukin-2 receptor; inhibits activated T cells</td>
<td>Glucose intolerance; pulmonary edema; infusion reaction; gastrointestinal upset; skin reactions</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Monoclonal antibody</td>
<td>Targets CD20, a marker of immature B cells; depletes B-cell populations</td>
<td>PML (rate undefined); infusion-related side effects</td>
<td>No efficacy assessments available in pediatric MS</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Chemotherapeutic</td>
<td>Disrupts purine metabolism; effects include cytotoxic immune cell depletion</td>
<td>Transaminitis; leukopenia; lymphoma</td>
<td>No efficacy assessments available in pediatric MS</td>
</tr>
<tr>
<td>Fingolimod†</td>
<td>Immunomodulator</td>
<td>Sphingosine-1-phosphate agonist; causes T-cell sequestration in lymphoid compartments</td>
<td>Systemic viral infection; cardiac arrhythmia; macular edema; transaminitis</td>
<td>FDA approved for adult MS in September 2010; no reports of use in pediatric MS to date</td>
</tr>
<tr>
<td>Teriflunomide*</td>
<td>Immunomodulator</td>
<td>Impairs immune cell proliferation via pyrimidine synthesis inhibition</td>
<td>Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity</td>
<td>FDA approved for adult MS in September 2012; no reports of use in pediatric MS to date</td>
</tr>
<tr>
<td><strong>EMERGING THERAPIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D†</td>
<td>Vitamin/hormone</td>
<td>Modulates immune cell expression</td>
<td>Hypercalcaemia and kidney stones at a serum 25(OH) vitamin D level &gt;100 ng/mL</td>
<td>Prospective trials in pediatric and adult MS are currently underway</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Monoclonal antibody</td>
<td>Targets CD20, a marker of immature B cells; depletes B-cell populations</td>
<td>Headache; infusion-related side effects; theoretical risk of PML (undefined)</td>
<td>Recently completed phase III trial in adult MS; no use in pediatric MS to date</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Immunomodulator</td>
<td>Neuroprotectant; antioxidant</td>
<td>Flushing reaction; gastrointestinal upset; headache</td>
<td>FDA approved for adult MS in March 2013; no use in pediatric MS to date</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Monoclonal antibody</td>
<td>Anti-CD52 antibody target; depletes mature T cells</td>
<td>Opportunistic infection, autoimmune thyroiditis (20-30% risk), immune thrombocytopenia (1%)</td>
<td>Recently completed phase III trial in adult MS; no use in pediatric MS to date</td>
</tr>
<tr>
<td>Laquinimod†</td>
<td>Immunomodulator</td>
<td>Modulates T cell and cytokine production</td>
<td>Transaminitis</td>
<td>Recently completed phase III trial in adult MS; no use in pediatric MS to date</td>
</tr>
</tbody>
</table>

*FDA approved for the treatment of adult MS.
†Orally administered therapy.
CNS, central nervous system; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.
LABORATORY FINDINGS
CSF in patients with NMO often has 50 or more white blood cells per microliter. Unlike MS, it is devoid of oligoclonal bands. Serum positivity for anti–aquaporin-4 antibodies (so-called NMO antibodies) has a sensitivity of 73% and a specificity of 91% for NMO. Neuroimaging studies should include the entire spine, optic nerves as well as the cortex that may reveal lesions in the brainstem or thalamus or hazy ill-defined lesions in the hemispheres in contrast to the discrete, well-defined oval lesions in the periventricular white matter seen in MS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
Clinical diagnosis of NMO currently requires optic neuritis and transverse myelitis plus at least 2 of 3 supporting criteria: (1) brain MRI not diagnostic of MS, (2) seropositivity for anti–aquaporin-4 antibody, or (3) spine MRI with longitudinally extensive transverse myelitis involving at least 3 spinal segments (see Table 600-2). NMO spectrum disorder may be diagnosed in relapsing forms of transverse myelitis or optic neuritis with aquaporin-4 seropositivity. The differential diagnosis includes MS; ADEM (see Chapter 600.3); rheumatologic etiologies producing transverse myelitis, and/or optic neuritis, including systemic lupus erythematosus, Behçet disease, and neurosarcoidosis (usually accompanied by other nonneurologic manifestations); idiopathic transverse myelitis, tropical spastic paraparesis, and viral encephalomyelitis (none of which have NMO antibodies in the serum or CSF); and metabolic and idiopathic causes of isolated optic neuritis or other acute monocular or binocular visual loss (see Chapter 631). Additional considerations depending on the location of the lesions include lymphoma, Langerhans cell histiocytosis, tuberculosis, and vitamin B12 or E deficiencies.

COMPLICATIONS
Similar to adults with NMO, pediatric NMO patients often are left with fixed neurologic deficits affecting visual acuity, visual fields, color vision, motor and sensory function, balance, and bowel/bladder function.

TREATMENT
Initial episodes and relapses may be treated acutely with methylprednisolone, 20–30 mg/kg/day (max: 1,000 mg/day) for 3–5 days, followed by a slow prednisone taper. Rituximab is effective in preventing relapses of NMO and NMO spectrum disorder. Preliminary evidence suggests that eculizumab also reduced recurrences and may improve disability in patients with severe NMO spectrum disorder.

PROGNOSIS
The prognosis is generally poor for patients with NMO. In 1 study, approximately 20% remained functionally blind (i.e., 20/200 vision or worse) in at least 1 eye and 31% had permanent monoplegia or paraplegia. Five-year survival of the patients with paraplegia is approximately 90%.

Bibliography is available at Expert Consult.

600.3 Acute Disseminated Encephalomyelitis

ADEM is an initial inflammatory, demyelinating event with multifocal neurologic deficits, typically accompanied by encephalopathy (see Table 600-2).

EPIDEMIOLOGY
ADEM can occur at any age but most series report a mean age between 5 and 8 yr with a slight male predominance. Reported incidence ranges from 0.07-0.4 per 100,000 per year in the pediatric population.

PATHOGENESIS
Molecular mimicry induced by infectious exposure or vaccine may trigger production of CNS autoantigens. Many patients experience a transient febrile illness in the month prior to ADEM onset. Preceding infections associated with ADEM include influenza, Epstein-Barr virus, cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex, and Mycoplasma pneumoniae. Postvaccination ADEM has been reported following immunizations for rabies, smallpox, measles, mumps, rubella, Japanese encephalitis B, pertussis, diphtheria-polio-tetanus, and influenza.

CLINICAL MANIFESTATIONS
Initial symptoms of ADEM may include lethargy, fever, headache, vomiting, meningeal signs, and seizures, including status epilepticus. Encephalopathy is a hallmark of ADEM, ranging from ongoing confusion to persistent irritability to coma. Focal neurologic deficits can be difficult to ascertain in the obtunded or very young child but common neurologic signs in ADEM include visual loss, cranial neuropathies, ataxia, motor and sensory deficits, plus bladder/bowel dysfunction with concurrent spinal cord demyelination.

NEUROIMAGING
Head CT may be normal or show hypodense regions. Cranial MRI, the imaging study of choice, typically exhibits large, multifocal and sometimes confluent or large edematous mass-like tumefactive T2 lesions with variable enhancement within white and often gray matter of the cerebral hemispheres, cerebellum, and brainstem (Fig. 600-2). Deep gray-matter structures (thalamus, basal ganglia) are often involved, although this may not be specific to ADEM. Spinal cord may have abnormal T2 signal or enhancement, with or without clinical signs of myelitis. MRI lesions of ADEM typically appear to be of similar age but their evolution may lag behind the clinical presentation. Serial MRI imaging 3-12 mo following ADEM shows improvement and often complete resolution of T2 abnormalities, although residual gliosis may remain.

Figure 600-2 Axial T2-weighted fluid-attenuated inversion recovery MRI of the brain in a child with acute disseminated encephalomyelitis. High signal (white) lesions in the T2-weighted image reflect areas of demyelination and edema in deep subcortical and periventricular white matter as well as the basal ganglia and thalamus on the left side.
Bibliography
Severe involvement may progress to an **acute hemorrhagic leukoencephalopathy (Hurst disease)** with large lesions, edema, mass affect, and a polymorphonuclear cell pleocytosis (in contrast to lymphocytic pleocytosis in the CSF noted in typical ADEM) (Fig. 600-3).

**LABORATORY FINDINGS**

There is no biologic marker for ADEM and laboratory findings can vary widely. CSF studies often exhibit pleocytosis with lymphocytic or monocytic predominance. CSF protein can be elevated, especially on repeat studies. Up to 10% of patients with ADEM have oligoclonal bands in the CSF and/or elevated CSF immune globulin production. Patients with ADEM may occasionally demonstrate antibodies against myelin oligodendrocyte glycoprotein, or anti-N-methyl-D-aspartate receptor antibodies. Electroencephalograms often show generalized slowing, consistent with encephalopathy, although polyregional demyelination of ADEM can also cause focal slowing or epileptiform discharges.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for ADEM is broad but can be narrowed by careful history, appropriate laboratory evaluations, and MRI (see Table 600-1). Empirical antibiotic and antiviral treatment should be considered while infectious evaluations are pending. Follow-up MRI examinations 3-12 mo after ADEM should show improvement; new or enlarging T2 lesions should prompt reevaluation for other etiologies such as MS, leukodystrophies, tumor, vasculitis, or mitochondrial, metabolic, or rheumatologic disorders (see Table 600-1 and Table 600-5).

**TREATMENT**

Although there are no randomized controlled trials to compare acute treatments for ADEM or other demyelinating disorders of childhood, high-dose intravenous steroids are commonly employed (typically methylprednisolone 20-30 mg/kg per day for 5 days with a maximum dose of 1,000 mg per day). An oral prednisone taper over 1 mo may prevent relapse. Other treatment options include intravenous immune globulin (usually 2 g/kg administered over 2-5 days) or plasmapheresis (typically 5-7 exchanges administered every other day). In severe cases of suspected ADEM, rituximab or cyclophosphamide have been used. There is no consensus about timing of these treatments for ADEM.

**PROGNOSIS**

Many children experience full recovery after ADEM but some are left with residual motor and/or cognitive deficits. ADEM is usually a monophasic illness but demyelinating symptoms can fluctuate for several months. Repeated bouts of demyelination more than 3 mo after ADEM later raise the question of MS vs repeated ADEM.
Bibliography
Stroke is an important cause of acquired brain injury in newborns and children. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are more common than brain malignancy (incidence approximately 5 in 100,000 children per year). Perinatal stroke is even more common and is the leading cause of hemiparetic cerebral palsy. A similar number of children suffer from hemorrhagic stroke (HS) and other forms of cerebrovascular disease. Acute stroke is a neurologic emergency; however, delays in recognition are common and delayed treatment worsens outcomes. In contrast to stroke in adults, there are a diverse group of disorders producing stroke in neonates and children.

601.1 Arterial Ischemic Stroke

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of Willis. Strokes most often involve the middle cerebral artery territory but can occur in any cerebral artery of any size. AIS is the focal brain infarction that results from occlusion of these arteries and is the leading cause of acquired brain injury in children with the perinatal period carrying the highest risk.

The diagnosis of stroke in children is frequently delayed. This is a consequence of subtle and nonspecific clinical presentations, poor awareness by primary care pediatric physicians, a complicated differential diagnosis (see Chapter 601.4), and a high frequency (>50%) of negative initial CT scan. The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise. The most common focal presentation is hemiparesis, but acute visual, speech, sensory, or balance deficits also occur. Children with these presentations require urgent neuroimaging and consultation with a child neurologist, as emergency interventions may be indicated. AIS is a clinical and radiographic diagnosis. Although CT imaging can demonstrate mature AIS and exclude hemorrhage, MRI is required to identify early and small infarcts. Diffusion-weighted MRI demonstrates AIS within minutes of onset and up to 7 days postonset; MR angiography can confirm vascular occlusion and suggest possible arteriopathy (Fig. 601-1). Diffusion-weighted MRI can also demonstrate wallerian degeneration
The Nervous System

Surface vessels. Arterial dissection can be spontaneous or post-traumatic and can affect extra- or intracranial arteries. Moyamoya syndrome may be idiopathic or associated with other conditions (neurofibromatosis type 1, trisomy 21, Alagille syndrome, sickle cell anemia, chromosomal microdeletions/microduplications, postirradiation) and demonstrates progressive occlusion of the distal internal carotid arteries. Congenital malformations of the craniocervical arteries, including PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, or fibromuscular dysplasia may predispose to AIS. Vasospasm as occurs in migraine, subarachnoid hemorrhage or reversible cerebral vasoconstriction syndrome (sometimes called Call-Fleming syndrome) can cause AIS. Cardioembolic stroke makes up approximately 25% of childhood AIS with maximal embolic risk concurrent with catheterization, surgical repair, or ventricular assistive device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries and reoperation increases the risk. Although complex congenital heart diseases are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, also should be considered. A patent foramen ovale provides the possibility of paradoxical venous thromboembolism but is not likely an independent risk factor. All children with suspected AIS require thorough cardiovascular examination, electrocardiogram, and echocardiogram.

Figure 601-1 Arterial ischemic stroke. A healthy 3 yr old boy had sudden onset of left-sided weakness. Examination also demonstrated left-sided hemisensory loss and neglect. A to C, Diffusion-weighted MRI shows focal increased signal in the right temporal–parietal region in the territory of the middle cerebral artery (MCA). D, Apparent diffusion coefficient map confirms restricted diffusion consistent with infarction (ischemic stroke). E, MR angiogram shows decreased flow in the corresponding branch of the MCA. F, Follow-up MRI at 3 mo shows atrophy and gliosis in the same region.

in the descending corticospinal tract, which correlates with chronic hemiparesis.

Many possible risk factors for AIS are recognized (Table 601-1), although the specific pathophysiologic mechanisms are often poorly understood. Three main categories of etiology should be considered: arteriopathy, cardiac, and hematologic; full investigation, however, often reveals multiple risk factors per individual.

Arteriopathy refers to disorders of the cerebral arteries and is a leading cause of childhood AIS, present in more than 50% of children. A common syndrome affecting healthy school-age children features unilateral irregular stenosis of the proximal middle cerebral artery and neighboring arteries presenting with basal ganglia infarction. The description of this entity has been published under multiple names—transient cerebral arteriopathy, postvaricella angiopathy, nonprogresive childhood primary angitis of the central nervous system, and focal cerebral arteriopathy—reflecting uncertainty regarding the pathogenesis.

This entity may represent focal inflammation or intracranial dissection or early moyamoya disease, although it is nearly always self-limited. Diffuse, bilateral, progressive vasculitis is rare and can represent progressive childhood primary angitis of the central nervous system or be associated with systemic vasculitides (Table 601-2). Cranial infections (e.g., bacterial meningitis) also produce arteritis and thrombophlebitis of surface vessels. Arterial dissection can be spontaneous or post-traumatic and can affect extra- or intracranial arteries. Moyamoya syndrome may be idiopathic or associated with other conditions (neurofibromatosis type 1, trisomy 21, Alagille syndrome, sickle cell anemia, chromosomal microdeletions/microduplications, postirradiation) and demonstrates progressive occlusion of the distal internal carotid arteries. Congenital malformations of the craniocervical arteries, including PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, or fibromuscular dysplasia may predispose to AIS. Vasospasm as occurs in migraine, subarachnoid hemorrhage or reversible cerebral vasoconstriction syndrome (sometimes called Call-Fleming syndrome) can cause AIS.

Cardioembolic stroke makes up approximately 25% of childhood AIS with maximal embolic risk concurrent with catheterization, surgical repair, or ventricular assistive device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries and reoperation increases the risk. Although complex congenital heart diseases are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, also should be considered. A patent foramen ovale provides the possibility of paradoxical venous thromboembolism but is not likely an independent risk factor. All children with suspected AIS require thorough cardiovascular examination, electrocardiogram, and echocardiogram.
<table>
<thead>
<tr>
<th>MAJOR CATEGORY</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriopathy</td>
<td>Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA]); Postvaricella and other viruses angiopathy (PVA); Systemic/secondary vasculitis (e.g., Takayasu arteritis); Moyamoya disease/syndrome; Arterial infection (e.g., bacterial meningitis, tuberculosis); Fibromuscular dysplasia; Traumatic or spontaneous carotid or vertebral artery dissection; Vasospasm (e.g., Call-Fleming syndrome); Migraine (migrainous infarction?); Congenital arterial hypoplasia (e.g., PHACES syndrome)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Complex congenital heart diseases (cyanotic &gt;&gt; acyanotic); Cardiac catheterization/procedure (e.g., balloon atrial septostomy); Ventricular assistive device use; Cardiac surgery; Arrhythmia; Valvular heart disease; Endocarditis; Cardiomyopathy, severe ventricular dysfunction; Intracardiac lesions (e.g., atrial myxoma); Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli])</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Sickle cell anemia; Iron-deficiency anemia; Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A); Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy)</td>
</tr>
<tr>
<td>Other including metabolic/genetic etiologies</td>
<td>Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis); Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia); Illicit drugs and toxins (e.g., cocaine); Extracorporeal membrane oxygenation (ECMO); Hereditary dyslipoproteinemia; Familial hypoalphalipoproteinemia; Familial hypercholesterolemia; Type IV, type III hyperlipoproteinemia; Tangier disease; Progeria; Fabry disease (α-galactosidase A deficiency); Subacute necrotizing encephalomyelopathy (Leigh disease); Sulfite oxidase deficiency; 11β-Ketoreductase deficiency; 17α-Hydroxylase deficiency; Purine nucleoside phosphorylase deficiency; Ornithine transcarbamylase deficiency; Neurofibromatosis type 1; HERNs; Heritable disorders of connective tissue; Ehlers-Danlos syndrome (type IV); Marfan syndrome; Pseudoxanthoma elasticum; Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase); Menkes syndrome; Organic acidemias; Methylmalonic academia; Propionic academia; Isovaleric academia; Glutaric aciduria type II; Mitochondrial encephalomyopathies; MELAS; MERRF; MERRF/MELAS overlap syndrome; Kears-Sayre syndrome; See also: stroke mimics (see Chapter 601.4)</td>
</tr>
</tbody>
</table>

HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

Prothrombotic coagulation disorders and infection at index stroke increase stroke recurrence risk.

Hematologic disorders associated with AIS include sickle cell anemia, in which stroke risk is increased 400-fold, although effective screening (transcranial Doppler) and treatments (transfusions) have reduced the incidence. Iron-deficiency anemia also increases the risk and is easily treatable. Coagulation disorders are associated with childhood AIS. They include hereditary (e.g., factor V Leiden) and acquired (e.g., antiphospholipid antibodies, lipoprotein-a elevation) prothrombotic states and prothrombotic medications, including oral contraceptives and aspiraginase chemotherapy. Additional AIS risk factors include migraine, acute childhood illnesses, chronic systemic illnesses, illicit drugs and toxins, and rare inborn errors of metabolism.

Treatment of childhood AIS is multifaceted and multiple consensus-based guidelines are available. Given the inadequate safety data, emergency thrombolysis is not recommended for children, but safety studies are underway. Early initiation of antithrombotic strategies is paramount to prevent early reinfarction. Depending on the suspected cause, this includes anticoagulation with heparins or antiplatelet strategies, usually aspirin. Hyperacute neuroprotective strategies are essential to initiate with suspected stroke as they prevent progressive ischemic brain injury. These include control of blood glucose, temperature and seizures and maintenance of cerebral perfusion pressure. Early malignant cerebral edema is life-threatening, more common in children and predictable, and emergency surgical decompression can be life-saving. Disease-specific treatments include transfusion therapy in sickle cell disease, immunosuppression in vasculitis, and revascularization surgery in moyamoya. Long-term treatment goals include secondary stroke prevention, including antplatelet therapy in arteriopathy and anticoagulation in cardiogenic causes. Multimodal, family-centered rehabilitation programs are required for most survivors, targeting motor deficits, language and intellectual impairments, behavioral and social disabilities, and epilepsy. Long-term attention to arterial health lifestyle factors may also be important. Outcomes after childhood stroke include recurrent stroke ranging from 10-50% depending on cause and preventative treatment, death in 6-10%, neurologic deficits in 60-70%, and seizure disorders in up to 30%.

**PERINATAL ARTERIAL ISCHEMIC STROKE**

Perinatal stroke is very common, differs from childhood stroke, and has 2 distinct clinical presentations. Acute symptomatic neonatal AIS presents with focal seizures at 24-28 hr of life (Fig. 601-2). MRI diffusion

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**Table 601-2 Classification of Cerebral Vasculitis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious vasculitis</td>
<td>Bacterial, fungal, parasitic, Spirochetal (syphilis, Lyme disease, leptospirosis)</td>
</tr>
<tr>
<td></td>
<td>Viral, rickettsial, mycobacterial, free-living amebeae, cysticercosis, other helminths</td>
</tr>
<tr>
<td>Necrotizing vasculitides</td>
<td>Classic polyarteritis nodosa, Wegener granulomatosis, Allergic angiitis and granulomatosis (Churg-Strauss syndrome)</td>
</tr>
<tr>
<td></td>
<td>Necrotizing systemic vasculitis overlap syndrome, Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Vasculitis associated with collagen vascular disease</td>
<td>Systemic lupus erythematosus, Rheumatoid arthritis, Scleroderma, Sjögren syndrome</td>
</tr>
<tr>
<td>Vasculitis associated with other systemic diseases</td>
<td>Behçet disease, Ulcerative colitis, Sarcoidosis, Relapsing polychondritis, Kohlmeier-Degos disease, Takayasu arteritis</td>
</tr>
<tr>
<td>Hypersensitivity vasculitides</td>
<td>Henoch-Schönlein purpura, Drug-induced vasculitides, Chemical vasculitides</td>
</tr>
<tr>
<td>Essential mixed cryoglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Vasculitis associated with neoplasia, Vasculitis associated with radiation, Cogan syndrome, Dermatomyositis-polymyositis, X-linked lymphoproliferative syndrome, Kawasaki disease</td>
</tr>
</tbody>
</table>

Primary central nervous system vasculitis  


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**Figure 601-2** Perinatal arterial ischemic stroke. A term newborn developed focal right-sided seizures at 16 hr of life. A, Diffusion-weighted MRI on day 2 diagnoses neonatal arterial ischemic stroke by demonstrating restricted diffusion in the left middle cerebral artery territory. B, Repeat MRI at 12 mo shows cystic encephalomalacia and scarring in the same territory, a similar appearance to children diagnosed with presumed perinatal arterial ischemic stroke later in infancy.
abnormalities in an arterial territory confirm recent infarction. Alternatively, infants are asymptomatic at birth and present in later infancy with signs of early hand preference and congenital hemiparesis. Hand dominance within the 1st yr of life is abnormal and may be the result of perinatal stroke. Imaging reveals focal encephalomalacia in an arterial territory, typically large middle cerebral artery lesions.

In acute neonatal AIS, seizure control is important, but antithrombotic agents are rarely required (exception: cardiac embolism). Pathophysiology is complex and poorly understood. Most are idiopathic, although established causes include congenital heart disease, thrombotic placentalpathy, and other prothrombotic disorders and meningi-tis. Many other maternal, prenatal, perinatal, obstetrical, and neonatal factors have been investigated with several strong associations found (e.g., infertility, primiparity, multiple gestation). Outcomes are poor, with most children having lifelong disability. Perinatal stroke accounts for most cases of hemiparetic cerebral palsy (congenital hemiplegia, see Chapter 598.1). Additional morbidity, seen in approximately 25%, includes disorders of language, learning, cognition, and behavior and longer-term epilepsy. Stroke recurrence rates for both the child and subsequent pregnancies are extremely low.

Bibliography is available at Expert Consult.

601.2 Cerebral Sinovenous Thrombosis
Adam Kirton and Gabrielle A. deVeber

Cerebral venous drainage occurs via the cerebral sinovenous system. This includes superficial (cortical veins, superior sagittal sinus) and deep (internal cerebral veins, straight sinus) systems that converge at the torcular to exit via the paired transverse and sigmoid sinuses and jugular veins. In CSVT, thrombotic occlusion of these venous structures can create increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction or hemorrhage (stroke). CSVT may be more common in children than in adults, and risk is greatest risk in the neonatal period.

Clinical presentations are typically gradual, variable, and nonspecific compared to AIS. Neonates often present with encephalopathy and seizures. Children may present with symptoms mimicking idiopathic intracranial hypertension, including progressive headache, papilledema, diplopia secondary to 6th nerve palsy, or with acute focal deficits. Seizures, lethargy, and confusion are common. Diagnosis requires a high clinical suspicion and purposeful imaging of the cerebral venous system. Nonenhanced CT is very insensitive for CSVT, and contrast CT venography or MR venography is necessary to demonstrate filling defects in the cerebral venous system (Fig. 601-3). MRI offers superior parenchymal imaging compared to CT.

Table 601-3 lists the risk factors for CSVT. Prothrombotic states associated with childhood CSVT include inherited (e.g., prothrombin gene 20210A mutation) and acquired (e.g., antiphospholipid antibodies) conditions, prothrombotic medications (asparaginase, oral contraceptives) and common childhood illnesses including otitis media, iron-deficiency anemia, and dehydration. Systemic diseases associated with increased CSVT risk include leukemia, inflammatory bowel disease, and nephrotic syndrome.

Head and neck disorders can directly involve cerebral veins and sinuses causing CSVT. Common infections, including meningitis, otitis media, and mastoiditis, can cause septic thrombophlebitis of venous channels. CSVT can complicate head trauma especially adjacent to skull fractures. Neurosurgical procedures in proximity to cerebral venous structures may lead to injury and CSVT. Finally, obstruction of the jugular veins and proximal stasis may result in CSVT. In neonates, the unfused status of cranial sutures enables mechanical distortion of underlying venous sinuses during delivery, or postnatally occipital bone compression of the posterior sagittal sinus during supine lying predisposing to CSVT.

Anticoagulation therapy plays an important role in childhood CSVT treatment. Substantial indirect evidence has led to consensus to recommend anticoagulation with unfractionated or low-molecular-weight heparins in most children. Hemorrhagic transformation of venous infarcts is not an absolute contraindication. Treatment is usually planned for 6 mo, although if reimaging at 3 mo confirms recanalization, treatment is usually discontinued. However anticoagulation of neonates is more controversial and guidelines differ. Evidence suggests that 30% of untreated neonates and children will extend their thrombosis in the 1st wk postdiagnosis and additional venous infarction can result. Therefore, if anticoagulation is withheld, early (e.g., 5-7
Bibliography

Bibliography is available at Expert Consult.

601.3 Hemorrhagic Stroke

Adam Kirton and Gabrielle A. deVeber

HS includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location, whereas intraventricular hemorrhage may be isolated or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces.

Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or thunderclap headache, loss of consciousness, and nuchal rigidity in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus, cranial bruit, macrocephaly, and high-output heart failure may be present. Diagnosis relies on imaging and CT is highly sensitive to acute HS. However, lumbar puncture may be required to exclude subarachnoid hemorrhage. MRI is highly sensitive to even small amounts of both acute and chronic hemorrhage and offers improved diagnostic accuracy (Fig. 601-4). Angiography by CT, MR, or conventional catheter means is often required to exclude underlying vascular abnormalities (e.g., vascular malformations, aneurysms).

Abusive head trauma with intracranial bleeding in children may present as primary subdural or parenchymal hemorrhage with no apparent history of trauma. Subtle scalp, suborbital, or ear bruising; retinal hemorrhages in multiple layers; and chronic failure to thrive should always be sought, and in infants with subdural bleeds, x-rays performed to rule out fractures. Epidural hematoma is nearly always caused by trauma, including middle meningeal artery injury typically associated with skull fracture. Subdural hematoma can occur spontaneously in children with brain atrophy because of stretching of bridging veins.

Causes of and risk factors for HS (Table 601-4) include vascular malformations and systemic disorders. Arteriovenous malformations

<table>
<thead>
<tr>
<th>Table 601-3</th>
<th>Common Risk Factors for Cerebral Sinovenous Thrombosis in Children</th>
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<tbody>
<tr>
<td><strong>MAJOR CATEGORIES</strong></td>
<td><strong>EXAMPLES</strong></td>
</tr>
<tr>
<td>Blood coagulation</td>
<td>Prothrombotic conditions</td>
</tr>
<tr>
<td></td>
<td>Dehydration (e.g., gastroenteritis, neonatal failure to thrive)</td>
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<td></td>
<td>Iron-deficiency anemia</td>
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<tr>
<td></td>
<td>Drugs and toxins (e.g., L-asparaginase, oral contraceptives)</td>
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<tr>
<td></td>
<td>Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation)</td>
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<tr>
<td></td>
<td>Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia)</td>
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<td>Nephrotic syndrome</td>
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<td>Inborn errors of metabolism (e.g., homocystinuria)</td>
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<tr>
<td>Blood vessel</td>
<td>Infection/thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis</td>
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<tr>
<td></td>
<td>Lemierre syndrome</td>
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<tr>
<td></td>
<td>Sepsis</td>
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<tr>
<td></td>
<td>Trauma: skull fractures, closed head trauma</td>
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<tr>
<td></td>
<td>Compression: birth, occipital bone compression in neonates in supine lying</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation</td>
</tr>
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<td>Venous malformations (e.g., dural arteriovenous fistulas)</td>
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</table>

<table>
<thead>
<tr>
<th>Table 601-4</th>
<th>Potential Risk Factors for Hemorrhagic Stroke in Children</th>
</tr>
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<tbody>
<tr>
<td><strong>MAJOR CATEGORIES</strong></td>
<td><strong>EXAMPLES</strong></td>
</tr>
<tr>
<td>Vascular disorder</td>
<td>Arteriovenous malformations</td>
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<tr>
<td></td>
<td>Cavernous malformations (“cavernomas”)</td>
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<tr>
<td></td>
<td>Venous angiomas and other venous anomalies</td>
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<tr>
<td></td>
<td>Hereditary hemorrhagic telangiectasia</td>
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<tr>
<td></td>
<td>Intracranial aneurysm</td>
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<tr>
<td></td>
<td>Choroid plexus angiomas (pure intraventricular hemorrhage)</td>
</tr>
<tr>
<td></td>
<td>Moyamoya disease/syndrome</td>
</tr>
<tr>
<td></td>
<td>Inflammatory vasculitis (see Chapter 601.1)</td>
</tr>
<tr>
<td></td>
<td>Neoplastic lesions with unstable vasculature</td>
</tr>
<tr>
<td></td>
<td>Drugs/toxins (cocaine, amphetamine)</td>
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<tr>
<td></td>
<td>Cerebral sinus venous thrombosis</td>
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<tr>
<td>Blood disorder</td>
<td>Idiopathic thrombocytopenic purpura</td>
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<td></td>
<td>Hemolytic uremic syndrome</td>
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<td></td>
<td>Hepatic disease/failure coagulopathy</td>
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<tr>
<td></td>
<td>Vitamin K deficiency (hemorrhagic disease of the newborn)</td>
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<td></td>
<td>Disseminated intravascular coagulopathy</td>
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<td>Trauma</td>
<td>Middle meningeal artery injury (epidural hematoma)</td>
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<tr>
<td></td>
<td>Bridging vein injury (subdural hematoma)</td>
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<td></td>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td></td>
<td>Hemorrhagic contusions (coup and contrecoup)</td>
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<tr>
<td></td>
<td>Nonaccidental trauma (subdural hematomas of different ages)</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (neurosurgical procedures, angiography)</td>
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<tr>
<td></td>
<td>Rupture of arachnoid cyst</td>
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</table>
**Bibliography**


Figure 601-4 Hemorrhagic stroke. A healthy 1 mo old presented with sudden-onset irritability followed by focal left body seizures. Plain CT head demonstrates a large hyperdense lesion in the right parietal region with surrounding edema consistent with acute hemorrhage (A). Axial (B) and sagittal (C) contrast CT scans suggest an abnormal cluster of vessels in the center of the hemorrhage consistent with an AVM. T2-weighted MRI differentiates the acute hemorrhage from surrounding edema (D). Gradient echo MRI, both acutely (E) and at 3 mo (F), demonstrates the presence of blood product.

are the most common cause of childhood subarachnoid and intraparenchymal HS and may occur anywhere. Neonates with vein of Galen malformations may present with heart failure, progressive macrocephaly, or, rarely, hemorrhage. In older children with arteriovenous malformations, the risk of bleeding is approximately 2-4% per year throughout life. Other vascular malformations leading to HS include cavernous angiomas ("cavernomas"), dural arteriovenous fistulas, and vein of Galen malformations. Cerebral aneurysms are an uncommon cause of subarachnoid hemorrhage in children and may suggest an underlying disorder (e.g., polycystic kidney disease, infective endocarditis). A common cause for HS is bleeding from a preexisting brain tumor. Arterial diseases that usually cause ischemic stroke, including fibromuscular dysplasia, vasculitis, and moyamoya, can also predispose to HS. Additional causes of parenchymal HS include hypertensive hemorrhage and hematologic disorders such as thrombocytopenic purpura, hemophilia, acquired coagulopathies (e.g., disseminated intravascular coagulopathy, liver failure), anticoagulant therapy (e.g., warfarin), or illicit drug use. Ischemic infarcts may undergo hemorrhagic transformation, particularly in CSVT, and may be difficult to differentiate from primary HS.

Management of acute childhood HS may require emergent neurosurgical intervention for large or rapidly expanding hemorrhage. The same principles of neuroprotection for vulnerable brain suggested in the ischemic stroke sections also apply to HS. Reversal of anticoagulant therapy (with, for example, vitamin K, fresh-frozen plasma) may be required, but the role of other medical interventions, such as factor VII, are unstudied in children. Recurrence risk for those with structural lesions is significant and serial imaging may be required. Definitive repair or removal of the vascular malformation may require a combined approach with interventional endovascular methods or neurosurgery. Outcomes from childhood HS are not well studied but likely depend on lesion size, location, and etiology. Compared with ischemic stroke, HS mortality is higher while long-term deficits are less common.

Neonatal HSs have unique features. Cranial ultrasound can detect many neonatal parenchymal bleeds, especially in the preterm infant where bleeds are located centrally within the cranium and include germinal matrix bleeding and intraventricular hemorrhage (see Chapter 99.3). Germinal matrix injury or bleeding may also occur in utero, resulting in periventricular venous infarction that becomes symptomatic in later infancy as congenital hemiparesis. Subarachnoid and subdural blood may be imaged in up to 25% of normal term newborns. Term HS is poorly studied and includes the etiologies listed above, although HS may be idiopathic in more than 50% of cases. Term intraventricular bleeding is often secondary to deep CSVT with specific management implications.

Bibliography is available at Expert Consult.
Bibliography


The diagnosis of stroke in childhood requires a high index of suspicion balanced with awareness of the differential diagnosis for stroke-like events (Table 601-5). Acute onset of a focal neurologic deficit should be considered stroke until proven otherwise and assessed with neuroimaging. However, pediatric stroke must be differentiated from other stroke-like disorders that may require their own urgent specific treatment.

**MIGRAINE**
Careful history and examination can often suggest migraine as the cause of acute focal deficits. Migraine auras should last between 5 and 60 min and resolve completely. Neurologic deficits associated with migraine typically evolve slowly compared with stroke, with sensory disturbance or weakness "marching" across body areas over minutes. Although evolution into a migrainous headache is expected, headache may also accompany acute infarction. Furthermore, a group of uncommon migraine subtypes can occur without headache and can more closely mimic stroke in children. These include familial hemiplegic migraine, basilar migraine, and migraine aura without headache.

Migraine can also (rarely) cause a stroke, referred to as migrainous infarction.

**SEIZURE**
Prolonged focal seizure activity is frequently followed by a period of focal neurologic deficit ("Todd's paresis") which typically resolves within an hour. Very rarely, focal seizures can manifest with only "negative" symptoms producing acute onset, focal neurologic deficits. A history of clonic jerks or tonic posturing at onset, a known past history of seizures, and electroencephalogram findings may be helpful. Imaging is required in all new cases of seizure with persisting Todd's paresis because stroke in children is often associated with seizures at onset.

**INFECTION**
Life-threatening and treatable brain infections, including bacterial meningitis and herpes encephalitis, can be mistaken for stroke. However, symptom onset in primary central nervous system infection is typically more gradual and less focal with fever as a consistent feature. Children with bacterial meningitis are at risk for both venous and arterial stroke.

**DEMYELINATION**
Acute disseminated encephalomyelitis, clinically isolated syndrome, multiple sclerosis, and other demyelinating conditions can present...
with acute focal neurologic deficits. Symptom onset and initial progression is more gradual (typically hours or days) compared with stroke onset (minutes). Multifocal deficits, or concurrent encephalopathy in the case of acute disseminated encephalomyelitis, would decrease the probability of stroke.

HYPOGLYCEMIA
Acute lowering of blood glucose levels can produce focal deficits mimicking stroke. New-onset hypoglycemia in otherwise healthy children is rare, but predisposing conditions include insulin-dependent diabetes, adrenal insufficiency, steroid withdrawal, and ketogenic diet.

GLOBAL HYPOXIC–ISCHEMIC ENCEPHALOPATHY
Generalized decreases in cerebral perfusion can produce focal areas of watershed brain infarction which can be asymmetric and mimic stroke. Watershed ischemic injury should be accompanied by recognized hypotension or conditions predisposing to low cerebral perfusion such as sepsis, dehydration, or cardiac dysfunction. Clinical presentations would involve more generalized and bilateral cerebral dysfunction compared to stroke and the anatomic location of the infarct is in typical bilateral watershed zones rather than a single arterial territory.

HYPERTENSIVE ENCEPHALOPATHY
The posterior reversible leukoencephalopathy syndrome is seen in children with hypertension, often in the context of an acute rise in blood pressure. Posterior regions are selectively involved, possibly resulting in symptoms of bilateral cortical visual dysfunction in addition to encephalopathy and seizures.

INBORN ERRORS OF METABOLISM
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS; see Chapter 598.2) are the classic examples, though other mitochondrial disease can mimic stroke. Features favoring MELAS would include a history of developmental regression, posterior (and often bilateral) lesions not respecting vascular territories on MRI, and elevated serum or cerebrospinal fluid lactate (MR spectroscopy). In contrast to these types of “metabolic infarction,” children with Fabry disease (see Chapter 613.6) and homocystinuria (see Chapter 85.4) are at risk of true ischemic stroke.

VESTIBULOPATHY/ATAXIA
Acute onset vertigo and/or ataxia can be confused with brainstem or cerebellar stroke. Simple bedside tests of vestibular function with otherwise intact brainstem functions are reassuring. This differential diagnosis includes acute vestibular neuronopathy, viral labyrinthitis, and the benign paroxysmal vertigos as well as acute cerebellar ataxia and episodic ataxias.

CHANNELopathies
An increasing number of nervous system ion channel mutations are described that feature sudden focal neurological deficits thereby mimicking stroke. These include the migraine syndromes mentioned above as well as a growing list of episodic ataxias. A strong family history raises suspicion but most require additional investigation.

ALTERNATING HEMIPLEGIA OF CHILDHOOD
Alternating hemiplegia of childhood typically presents in infancy with acute intermittent episodes of hemiplegia that alternate from 1 side of the body to the other. The hemiplegia persists for minutes to weeks and then resolves spontaneously. Choreaathetosis and dystonic movements are commonly observed in the hemiparetic extremity. Signs spontaneously regress with sleep but recur with awakening. Neuroimaging including MRA should be completed to exclude moyamoya disease. Alternating hemiplegia of childhood is linked to mutations in the ATP1A3 gene.
Autoimmune-mediated inflammatory brain diseases are recognized as an etiology for neurologic and neuropsychiatric symptoms in children and adults and include primary central nervous system (CNS) vasculitis, secondary CNS vasculitis, and autoimmune encephalitis (Fig. 602-1; see Chapter 598.4).

Primary angiitis of the CNS (PACNS) is recognized as the underlying etiology of a broad spectrum of neurologic and psychiatric symptoms in children. Criteria characteristic of childhood CNS vasculitis (cPACNS) include (1) newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 yr of age or younger, plus (2) angiographic and/or histologic evidence of vasculitis in the absence of (3) a systemic underlying condition known to cause or mimic the findings. Two broad categories of cPACNS are recognized based on the predominant vessel size affected: large/medium-vessel cPACNS and small-vessel cPACNS. Large/medium-vessel cPACNS is diagnosed on angiography demonstrating features of vessel wall inflammation, wall swelling and edema, and resulting luminal stenosis. Based on the clinical course and the corresponding distribution of vessel stenosis within the vascular tree of the CNS, children with large/medium-vessel cPACNS are classified as a monophasic, nonprogressive (NPcPACNS) or a progressive subtype (PcPACNS). The latter is characterized by chronic, progressive vessel wall inflammation affecting both proximal and distal vessel segments in 1 or both hemispheres. In contrast, NPcPACNS is a monophasic illness; vessel inflammation occurs in a characteristic distribution and is limited to the proximal vessel segments of the anterior and/or middle cerebral artery and/or distal internal carotid artery of 1 hemisphere. Small vessel cPACNS (SVcPACNS) is considered a progressive illness; the diagnosis is confirmed on brain biopsies because angiography is normal.

Secondary childhood CNS vasculitis can affect all cerebral vessel segments and can occur in the context of infections, rheumatic or other inflammatory conditions or as a result of systemic or local vascular irritation (Table 602-1). The neuropsychiatric manifestations of secondary CNS vasculitis are the same as those of primary CNS vasculitis. Secondary CNS vasculitis is distinguished from primary CNS vasculitis largely by the non-CNS manifestations of the underlying systemic vasculitic disease.

EPIDEMIOLOGY
The incidence and prevalence of primary CNS vasculitis is undetermined. In the past, the majority of children have been diagnosed at autopsy. Increased physician awareness, improved diagnostic markers, sensitive neuroimaging techniques, and brain biopsies have led to dramatically increased recognition and decreased mortality. Exploring the epidemiology of primary CNS vasculitis remains a challenge: the disease has many names including isolated angiitis of the CNS, transient cerebral angiitis, postvaricella angioitis, and focal cerebral arteriopathy. Furthermore, children are frequently diagnosed with their presenting clinical phenotype, such as stroke, movement disorder, hallucination, or cognitive decline. Within clinical phenotypes, such as arterial ischemic stroke or status epilepticus in children without preexisting epilepsy, cPACNS should be considered an important etiology.

CLINICAL MANIFESTATIONS
Recognition of childhood CNS vasculitis requires a very high level of suspicion; any neurologic or psychiatric presentation can be the result
of an underlying CNS vasculitis. The clinical phenotype may provide clues to the size of the primarily affected vessel segments and resulting cPACNS subtype: the majority of children with large/medium cPACNS present with arterial ischemic stroke features. Focal neurologic deficits, such as hemiparesis, facial droop, aphasia or any other distinct gross or fine motor deficits, may be the result of large vessel inflammation causing stenosis and decreased blood supply to the specific functional areas of the brain. Initially, these focal deficits wax and wane; they may even briefly resolve without therapeutic intervention and can therefore be easily overlooked. Headaches are a symptom of vascular disease in general and are commonly reported in cPACNS. New onset of vascular-type (e.g., migraine) headaches in children without any family history of migraine can serve as a diagnostic clue. Cognitive dysfunction in type (e.g., migraine) headaches in children without any family history may be the result of large/medium-vessel cPACNS with mild–moderately raised markers. Von Willebrand factor antigen, an endothelial cell–derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating diseases. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including high opening pressure, raised CSF cell count, typically with lymphocyte predominance, and raised CSF protein. Oligoclonal bands are seen in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see Chapter 598.4) is one of the key differential diagnoses of SVcPACNS.

Neuroimaging is a valuable diagnostic modality for cPACNS. Parenchymal lesions may be inflammatory or ischemic in nature and are best viewed on MRI including T2/fluid attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWI) (Fig. 602-2). CNS lesions in children with large/medium-vessel cPACNS are predominantly ischemic in nature and restricted to large vascular territories. In contrast, MRI lesions in children with SVcPACNS are not restricted to major vascular territories; lesions are primarily inflammatory and may enhance with contrast. In this subtype, focal or is a disconnection between the clinical presentation and the child's electroencephalogram findings. In many centers, refractory status epilepticus is increasingly recognized as the presenting phenotype of SVcPACNS. Optic neuritis and spinal cord disease are also recognized in SVcPACNS.

Constitutional features of fever or fatigue may point toward an underlying systemic illness causing a secondary CNS vasculitis. All children with suspected or confirmed CNS vasculitis require a careful assessment for a systemic illness. **DIAGNOSIS**

The first step is considering vasculitis as a possible underlying etiology of newly acquired neurologic deficits and/or psychiatric symptoms (Table 602-2). The likelihood of CNS vasculitis in general and a specific subtype of CNS vasculitis in particular depends on the demographic characteristics of the patient, the CNS and non-CNS features of the clinical presentation, the preceding symptoms, and the mode of onset of the disease. SVcPACNS is more commonly seen in girls of all ages, whereas large/medium cPACNS has a clear male preponderance. Seizures are a hallmark of SVcPACNS, whereas strokes often reflect large/medium-vessel inflammation. Laboratory markers of vasculitis typically include C-reactive protein, erythrocyte sedimentation rate, and complete blood counts. But inflammatory markers lack sensitivity and specificity in cPACNS, particularly when the CNS is involved in isolation. More than 50% of children with large/medium-vessel cPACNS have normal inflammatory markers at diagnosis. In contrast, the majority of children with SVcPACNS present with mild–moderately raised markers. Von Willebrand factor antigen, an endothelial cell–derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating diseases. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including high opening pressure, raised CSF cell count, typically with lymphocyte predominance, and raised CSF protein. Oligoclonal bands are seen in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see Chapter 598.4) is one of the key differential diagnoses of SVcPACNS.

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generalized meningeal enhancement is commonly seen if children are imaged prior to immunosuppressive therapy. Spinal cord parenchymal imaging is challenging; defining the nature of lesions is often difficult.

Evidence of vessel stenosis confirms the diagnosis in large/medium-vessel cPACNS subtypes; brain biopsies are not required. Important information about the disease activity can be obtained from post–gadolinium contrast studies of the vascular wall. The vessel wall of an inflamed cerebral vessel in active large/medium-vessel cPACNS subtypes is thickened and enhances contrast. Conventional angiography when compared to MR angiography has a higher sensitivity in detecting vessel stenosis in the distal vessel segments, the posterior circulation, and in very young children. Vessel wall imaging is often normal in children with SVcPACNS, sometimes mandating an elective brain biopsy to definitively make the diagnosis. Studies of regional blood flow or therapeutic trials of antiinflammatory or immunosuppressive agents are nonsurgical alternatives that do not afford specific diagnostic information. Biopsies should target low-risk, nonfunctional areas identified on MRI. In the appropriate clinical context, nonlesional biopsies have a high yield for confirming the diagnosis of SVcPACNS. Characteristic findings in SVcPACNS include an intramural and/or perivascular mononuclear infiltrate, evidence of endothelial activation, and reactive astrocyte activation. Gliosis and perivascular demyelination are hallmarks of long-standing disease. Findings typically seen in adult PACNS, including granulomas or vessel wall necrosis, are rarely seen in children with SVcPACNS. In children, the diagnostic yield of brain biopsies is 70%. Biopsy-related complications are rarely seen.

Table 602-2 Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
   - Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
   - Seizures or (refractory) seizure status
   - Diffuse neurologic deficit including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
   - Headaches
   - Meningitis symptoms, abnormal level of consciousness
   - Psychiatric symptoms including hallucinations, pseudoseizures

**Differential diagnosis approach:**
   - Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features

2. Laboratory tests
   - Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
   - Endothelial markers: von Willebrand factor (vWF) antigen
   - Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

**Differential diagnosis approach:**
   - Infections/postinfectious inflammation: cultures, serologies, Gram stains
   - Autoimmune encephalitis: check neuronal antibodies in CSF and blood
   - Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
   - Thromboembolic conditions: procoagulatory profile

3. Neuroimaging
   - Parenchymal imaging on MRI:
     - Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium contrast (lesion enhancement)
     - Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping
   - Vessel imaging

4. Brain biopsy

Figure 602-2 Imaging of patients with primary CNS vasculitis. **A,** Cerebral angiogram shows alternating stenosis and dilation of the distal middle cerebral artery (arrows) and the anterior cerebral artery (arrowheads). **B,** Magnetic resonance angiography of the brain shows a short-segment stenosis of the anterior cerebral artery (green arrow) and stenosis of the distal middle cerebral artery (white arrow). **C,** Fluid attenuation inversion recovery–weighted MRI shows a large abnormality within the right cerebral hemisphere consistent with ischemia (arrowheads). **D,** MRI shows diffuse, asymmetric, nodular, and linear leptomeningeal enhancement, with dura only slightly affected. (FromSalvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis. Lancet 380:767–776, 2012, Fig. 2.)
Disorders that may be seen in adolescents and young adults that produce the reversible vasoconstriction syndrome must also be considered. These include migraine, drug-induced vasospasm, and postpartum angiopathy. Differentiating vasculitis is important for therapy and prognosis (Table 602-3).

**TREATMENT**

Corticosteroids are the mainstay of acute immunosuppressive management of cPACNS. Usually IV pulse therapy is initially given. Anti-thrombotic therapy is equally important, particularly in large/medium-vessel cPACNS subtypes, because children are at high risk for recurrent ischemic events. For the distinct cPACNS subtypes, different treatment regimens should be considered. Nonprogressive cPACNS is a monophasic inflammatory attack with the highest risk of poor neurologic outcome. Vessel wall inflammation causes severe proximal stenosis and a high restroke risk. High-dose corticosteroid pulses are commonly given followed by a 6-12 wk course of oral steroids at tapering doses. Second-line immunosuppressive agents are uncommonly used. All children require antithrombotic therapy. No unifying regimen exists. Many centers initially use low-molecular-weight heparin followed by long-term antiplatelet therapy. When reimaged at 3 mo follow-up, children should have stable or improved vessel disease, no newly affected vessel segments, and no evidence of contrast wall enhancement. At this point the immunosuppressive therapy is commonly discontinued and children are only kept on antiplatelet agents.

Progressive cPACNS and SVCcPACNS are considered chronic progressive vasculitis subtypes requiring a prolonged course of combination immunosuppression. High-dose corticosteroids are initially used followed by long-term oral corticosteroids with slow taper. Many centers use an induction-maintenance protocol adding IV cyclophosphamide to the corticosteroids as the induction medication, followed by mycophenolate mofetil or other oral second-line agents during maintenance therapy. Symptomatic therapy is essential including anticonvulsants or psychotropic medication if required. Supportive therapy includes bone protection with calcium and vitamin D, prophylaxis against pneumocystis pneumonia, and gastric mucosal protection as required.

**PROGNOSIS**

The mortality rate of cPACNS has significantly improved. Some treatment protocols for SVCcPACNS report a good outcome, defined as no functional neurologic deficits in two-thirds of children. Children presenting with status epilepticus and SVCcPACNS have the poorest cognitive outcome.

Bibliography is available at Expert Consult.
Bibliography


Infection of the central nervous system (CNS) is the most common cause of fever associated with signs and symptoms of CNS disease in children. Many microorganisms can cause infection. Nonetheless, specific pathogens are identifiable and are influenced by the age and immune status of the host and the epidemiology of the pathogen. In general, viral infections of the CNS are much more common than bacterial infections, which, in turn, are more common than fungal and parasitic infections. Infections caused by rickettsiae (Rocky Mountain spotted fever, *Ehrlichia*) are relatively uncommon but assume important roles under certain epidemiologic circumstances. *Mycoplasma* spp. can also cause infections of the CNS, although their precise contribution is often difficult to determine.

Regardless of etiology, most patients with CNS infection have similar clinical manifestations. **Common symptoms** include headache, nausea, vomiting, anorexia, restlessness, altered state of consciousness, and irritability; most of these symptoms are nonspecific. **Common signs** of CNS infection, in addition to fever, include photophobia, neck pain and rigidity, obtundation, stupor, coma, seizures, and focal neurologic deficits. The severity and constellation of signs are determined by the specific pathogen, the host, and the area of the CNS affected.

Infection of the CNS may be diffuse or focal. Meningitis and encephalitis are examples of diffuse infection. Meningitis implies primary involvement of the meninges, whereas encephalitis indicates brain parenchymal involvement. Because these anatomic boundaries are often not distinct, many patients have evidence of both meningeal and parenchymal involvement and should be considered to have meningoencephalitis. Brain abscess is the best example of a focal infection of the CNS. The neurologic expression of this infection is determined by the site and extent of the abscess(es) (see Chapter 604).

The diagnosis of diffuse CNS infections depends on examination of cerebrospinal fluid (CSF) obtained by lumbar puncture (LP). Table 603-1 provides an overview of the expected CSF abnormalities with various CNS disorders.
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PRESSURE (mm H₂O)</th>
<th>LEUKOCYTES (mm³)</th>
<th>PROTEIN (mg/dL)</th>
<th>GLUCOSE (mg/dL)</th>
<th>COMMENTS</th>
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<tr>
<td>Normal</td>
<td>50-80</td>
<td>&lt;5, ≥75% Lymphocytes</td>
<td>20-45</td>
<td>&gt;50 (or 75% serum glucose)</td>
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<tr>
<td><strong>COMMON FORMS OF MENINGITIS</strong></td>
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<tr>
<td>Acute bacterial meningitis</td>
<td>Usually elevated</td>
<td>100-10,000 or more; usually 300-2,000; PMNs predominate</td>
<td>Usually 100-500</td>
<td>Decreased, usually &lt;40 (or &lt;50% serum glucose) Normal or decreased</td>
<td>Organisms usually seen on Gram stain and recovered by culture</td>
</tr>
<tr>
<td>Partially treated bacterial meningitis</td>
<td>Normal or elevated</td>
<td>5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time</td>
<td>Usually 100-500</td>
<td>Normal or decreased</td>
<td>Organisms may be seen on Gram stain Pretreatment may render CSF sterile. Antigen may be detected by agglutination test</td>
</tr>
<tr>
<td>Viral meningitis or meningoencephalitis</td>
<td>Normal or slightly elevated (80-150)</td>
<td>Rarely &gt;1,000 cells. Eastern equine encephalitis and lymphocytic choromeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course</td>
<td>Usually 50-200</td>
<td>Generally normal; may be decreased to &lt;40 in some viral diseases, particularly mumps (15-20% of cases)</td>
<td>HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF</td>
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<tr>
<td><strong>UNCOMMON FORMS OF MENINGITIS</strong></td>
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<tr>
<td>Tuberculous meningitis</td>
<td>Usually elevated</td>
<td>10-500; PMNs early, but lymphocytes predominate through most of the course</td>
<td>100-3,000; may be higher in presence of block</td>
<td>&lt;50 in most cases; decreases with time if treatment is not provided</td>
<td>Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. <em>Mycobacterium tuberculosis</em> may be detected by PCR of CSF</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>Usually elevated</td>
<td>5-500; PMNs early but mononuclear cells predominate through most of the course. <em>Cryptococcus meningitis</em> may have no cellular inflammatory response</td>
<td>25-500</td>
<td>&lt;50; decreases with time if treatment is not provided</td>
<td>Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection</td>
</tr>
<tr>
<td>Syphilis (acute) and leptospirosis</td>
<td>Usually elevated</td>
<td>50-500; lymphocytes predominate</td>
<td>50-200</td>
<td>Usually normal</td>
<td>Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive</td>
</tr>
<tr>
<td>Amebic (<em>Naegleria</em>) meningoencephalitis</td>
<td>Elevated</td>
<td>1,000-10,000 or more; PMNs predominate</td>
<td>50-500</td>
<td>Normal or slightly decreased</td>
<td>Mobile amebas may be seen by hanging-drop examination of CSF at room temperature</td>
</tr>
<tr>
<td><strong>BRAIN ABSCESSES AND PARAMENINGEAL FOCUS</strong></td>
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<tr>
<td>Brain abscess</td>
<td>Usually elevated</td>
<td>5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach &gt;100,000</td>
<td>75-500</td>
<td>Normal unless abscess ruptures into ventricular system</td>
<td>No organisms on smear or culture unless abscess ruptures into ventricular system</td>
</tr>
<tr>
<td>Subdural empyema</td>
<td>Usually elevated</td>
<td>100-5,000; PMNs predominate</td>
<td>100-500</td>
<td>Normal</td>
<td>No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid</td>
</tr>
<tr>
<td>Cerebral epidural abscess</td>
<td>Normal to slightly elevated</td>
<td>10-500; lymphocytes predominate</td>
<td>50-200</td>
<td>Normal</td>
<td>No organisms on smear or culture of CSF</td>
</tr>
<tr>
<td>Spinal epidural abscess</td>
<td>Usually low, with spinal block</td>
<td>10-100; lymphocytes predominate</td>
<td>50-400</td>
<td>Normal</td>
<td>No organisms on smear or culture of CSF</td>
</tr>
<tr>
<td>Chemical (drugs, dermoid cysts, myelography dye)</td>
<td>Usually elevated</td>
<td>100-1,000 or more; PMNs predominate</td>
<td>50-100</td>
<td>Normal or slightly decreased</td>
<td>Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids</td>
</tr>
</tbody>
</table>
603.1 Acute Bacterial Meningitis Beyond the Neonatal Period

Charles G. Prober and Roshni Mathew

Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children. This infection is associated with a high rate of acute complications and risk of long-term morbidity. The incidence of bacterial meningitis is sufficiently high in febrile infants that it should be included in the differential diagnosis of those with altered mental status and other evidence of neurologic dysfunction.

ETIOLOGY

The most common causes of bacterial meningitis in children older than 1 mo of age in the United States are Streptococcus pneumoniae and Neisseria meningitidis. Bacterial meningitis caused by S. pneumoniae and Haemophilus influenzae type b has become much less common in developed countries since the introduction of universal immunization against these pathogens beginning at 2 mo of age. Demonstrating the importance of vaccination, invasive H. influenzae disease was reported in Minnesota in 2008 in 5 children with no relationship to one another and who were partially or not immunized. It is the largest number of children with invasive H. influenzae in Minnesota since 1992. Infection caused by S. pneumoniae or H. influenzae type b must be considered in incompletely vaccinated individuals or those in developing countries. Those with certain underlying immunologic (HIV infection, immunoglobulin [Ig] G subclass deficiency) or anatomic (sphenoid dysfunction, cochlear defects or implants) disorders also may be at increased risk of infection caused by these bacteria.

Alterations of host defense resulting from anatomic defects or immune deficits also increase the risk of meningitis from less-common pathogens such as Pseudomonas aeruginosa, Staphylococcus aureus, coagulase-negative staphylococci, Salmonella spp., anaerobes, and Listeria monocytogenes.

EPIDEMIOLOGY

A major risk factor for meningitis is the lack of immunity to specific pathogens associated with young age. Additional risks include recent colonization with pathogenic bacteria, close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by N. meningitidis or H. influenzae type b, crowding, poverty, black or Native American race, and male gender. The mode of transmission is probably person-to-person contact through respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and H. influenzae type b (12 times) relative to that for pneumococcus.

Specific host defense defects as a result of altered immunoglobulin production in response to encapsulated pathogens may be responsible for the increased risk of bacterial meningitis in Native Americans and Eskimos. Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease. Splenic dysfunction (sickle cell anemia) or asplenia (caused by trauma or congenital defect) is associated with an increased risk of pneumococcal, H. influenzae type b (to some extent), and, rarely, meningococcal sepsis and meningitis. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of L. monocytogenes infections of the CNS.

A congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), and middle ear (stapedial foot plate) or inner ear fistulas (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage through a rupture of the meninges as a result of a basal skull fracture into the cribriform plate or paranasal sinus, is associated with an increased risk of pneumococcal meningitis. The risk of bacterial meningitis, caused by S. pneumoniae, in children with cochlear implants, used for the treatment of hearing loss, is more than 30 times the risk in the general U.S. population. Lumbosacral dermal sinus and meningocele are associated with staphylococcal, anaerobic, and Gram-negative enteric bacterial meningitis. CSF shunt infections increase the risk of meningitis caused by staphylococci (especially coagulase-negative species) and other low-virulence bacteria that typically colonize the skin.

Streptococcus pneumoniae

See Chapter 182.

The 7-valent pneumococcal protein polysaccharide conjugate vaccine (PCV7) was introduced into the routine vaccination schedule in 2000 and contained the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. These serotypes caused most of the invasive pneumococcal infections in the United States at that time. The vaccine led to a dramatic decrease in rates of invasive pneumococcal disease. However, an increase in invasive disease caused by serotypes not contained in the original vaccine, such as serotype 19A, was observed. As a result, a 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) was licensed in the United States in February 2010. PCV13 contains the serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A. This vaccine is recommended for routine administration to all children 2-59 mo of age. The PCV13 vaccine is given as a 4-dose series at 2, 4, 6, and 12-15 mo of age. The incidence of invasive pneumococcal infections

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont’d

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PRESSURE (mm H2O)</th>
<th>LEUKOCYTES (mm3)</th>
<th>PROTEIN (mg/dL)</th>
<th>GLUCOSE (mg/dL)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONINFECTIONCAUSES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Normal or elevated slightly</td>
<td>0-100; mononuclear</td>
<td>40-100</td>
<td>Normal</td>
<td>No specific findings</td>
</tr>
<tr>
<td>Systemic lupus erythematosus with CNS involvement</td>
<td>Slightly elevated</td>
<td>0-500; PMNs usually predominate; lymphocytes may be present</td>
<td>100</td>
<td>Normal or slightly decreased</td>
<td>No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF. Cytology may be positive</td>
</tr>
<tr>
<td>Tumor, leukemia</td>
<td>Slightly elevated to very high</td>
<td>0-100 or more; mononuclear or blast cells</td>
<td>50-1,000</td>
<td>Normal to decreased (20-40)</td>
<td>MRI adds to diagnosis</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Normal or elevated</td>
<td>~100 lymphocytes</td>
<td>Normal to elevated</td>
<td>Normal</td>
<td>Anti-NMDAR antibody–positive</td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td>Normal</td>
<td>~100 lymphocytes</td>
<td>Normal to elevated</td>
<td>Normal</td>
<td>MRI adds to diagnosis</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, N-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophil.
peaks in the 1st 2 yr of life, reaching rates of 228 per 100,000 in children 6-12 mo of age. Children with anatomic or functional asplenia secondary to sickle cell disease and those infected with HIV have infection rates that are 20-100-fold higher than in those of healthy children in the 1st 5 yr of life. Additional risk factors for contracting pneumococcal meningitis include otitis media, sinusitis, pneumonia, CSFotorhea or rhinorrhea, the presence of a cochlear implant, and chronic graft-versus-host disease following bone marrow transplantation.

**Neisseria meningitidis**

See Chapter 191.

Five serogroups of meningococcus—A, B, C, Y, and W-135—are responsible for disease. Meningococcal meningitis may be sporadic or may occur in epidemics. In the United States, serogroups B, C, and Y each account for approximately 30% of cases, although serogroup distribution varies by location and time. Epidemic disease, especially in developing countries, is usually caused by serogroup A. Cases occur throughout the year but may be more common in the winter and spring and following influenza virus infections. Nasopharyngeal carriage of *N. meningitidis* occurs in 1-15% of adults. Colonization may last weeks to months; recent colonization places nonimmune younger children at greatest risk for meningitis. The incidence of disease occurring in association with an index case in the family is 1%, a rate that is 1,000-fold the risk in the general population. The risk of secondary cases occurring in contacts at daycare centers is approximately 1 in 1,000. Most infections of children are acquired from a contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Children younger than 5 yr have the highest rates of meningococcal infection. A second peak in incidence occurs in persons between 15 and 24 yr of age. College freshmen living in dormitories have an increased incidence of infection compared to non-college-attending, age-matched controls.

The Centers for Disease Control and Prevention (CDC) recommends vaccination against meningococcus (types A, C, W, and Y) with 1 dose of a quadrivalent conjugate meningococcal vaccine between the ages of 11 and 12 yr and for persons 2 mo to 18 yr who are at increased risk for meningococcal disease. The CDC also has specific recommendations for meningococcal vaccination of infants at high risk of meningococcal infection as a consequence of complement pathway deficiencies. College freshmen living in dormitories who have not been previously vaccinated should also be vaccinated.

**Haemophilus influenzae Type B**

See Chapter 194.

Before universal *H. influenzae* type b vaccination in the United States, approximately 70% of cases of bacterial meningitis occurring in the 1st 5 yr of life were caused by this pathogen. Invasive infections occurred primarily in infants 2 mo to 2 yr of age; peak incidence was at 6-9 mo of age, and 50% of cases occurred in the 1st yr of life. The risk to children was markedly increased among family or daycare center contacts of patients with *H. influenzae* type b disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with blunt immunologic responses to vaccine (such as children with HIV infection) remain at risk for *H. influenzae* type b meningitis.

**PATHOLOGY AND PATHOPHYSIOLOGY**

A meningeval purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum, and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates), as may subdural effusions and, rarely, empyema. Perivascular inflammatory infiltrates also may be present, and the ependymal membrane may be disrupted. Vascular and parenchymal cerebral changes characterized by polymorphonuclear infiltrates extending to the subintimal region of the small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage, and, rarely, cerebral cortical necrosis in the absence of identifiable thrombosis have been described at autopsy. Cerebral infarction, resulting from vascular occlusion because of inflammation, vasospasm, and thrombosis, is a frequent sequela. Infarct size ranges from microscopic to involvement of an entire hemisphere.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of the presence of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be a nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and, possibly, increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villi or obstruction of the flow of fluid from the ventricles. ICP may exceed 300 mm H₂O cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus ICP) is <50 cm H₂O as a result of systemic hypotension with reduced cerebral blood flow. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP (see Chapter 359).

Hypotony of brain extracellular spaces may cause cytotoxic edema after cell swelling and lysis. Tentorial, falx, or cerebellar herniation does not usually occur because the increased ICP is transmitted to the entire subarachnoid space and there is little structural displacement. Furthermore, if the fontanels are still patent, increased ICP is not always dissipated.

Hydrocephalus can occur as an acute complication of bacterial meningitis. It most often takes the form of a communicating hydrocephalus caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus, there is interference with the normal resorption of CSF. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the aqueduct of Sylvius or the foramina of Magendie and Luschka.

**Raised CSF** protein levels are partly a result of increased vascular permeability of the blood–brain barrier and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually found in the later phase of acute bacterial meningitis. Hypoglycorrhachia (reduced CSF glucose levels) is attributable to decreased glucose transport by the cerebral tissue.

Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and transudation (subdural effusions). These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later psychomotor retardation.

**PATHOGENESIS**

Bacterial meningitis most commonly results from hematogenous dissemination of microorganisms from a distant site of infection; bacteremia usually precedes meningitis or occurs concomitantly. Bacterial colonization of the nasopharynx with a potentially pathogenic microorganism is the usual source of the bacteremia. There may be prolonged carriage of the colonizing organisms without disease or, more likely, rapid invasion after recent colonization. Prior or concurrent viral upper respiratory tract infection may enhance the pathogenicity of bacteria producing meningitis.

*N. meningitidis* and *H. influenzae* type b attach to mucosal epithelial cell receptors by pili. After attachment to epithelial cells, bacteria breach the mucosa and enter the circulation. *N. meningitidis* may be transported across the mucosal surface within a phagocytic vacuole after ingestion by the epithelial cell. Bacterial survival in the bloodstream is enhanced by large bacterial capsules that interfere with opsonic phagocytosis and are associated with increased virulence. Host-related developmental defects in bacterial opsonic phagocytosis also contribute to the bacteremia. In young, nonimmune hosts, the
defect may be from an absence of preformed IgM or IgG antcapsular antibodies, whereas in immunodeficient patients, various deficiencies of components of the complement or properdin system may interfere with effective opsonic phagocytosis. Splenic dysfunction may also reduce opsonic phagocytosis by the reticuloendothelial system.

Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extrathecal CSF and subarachnoid space. Bacteria rapidly multiply because the CSF concentrations of complement and antibody are inadequate to contain bacterial proliferation. Chemotactic factors then incite a local inflammatory response characterized by polymorphonuclear cell infiltration. The presence of bacterial cell wall lipopolysaccharide (endotoxin) of Gram-negative bacteria (H. influenzae type b, N. meningitis) and of pneumococcal cell wall components (teichoic acid, peptidoglycan) stimulates a marked inflammatory response, with local production of tumor necrosis factor, interleukin 1, prostaglandin E, and other inflammatory mediators. The subsequent inflammatory response is characterized by neutrophilic infiltration, increased vascular permeability, alterations of the blood–brain barrier, and vascular thrombosis. Meningitis-associated brain injury is not simply caused by viable bacteria but occurs as a consequence of the host reaction to the inflammatory cascade initiated by bacterial components.

Rarely, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis or may occur after introduction of bacteria via penetrating cranial trauma, dermal sinus tracts, or meningomycele.

**CLINICAL MANIFESTATIONS**
The onset of acute meningitis has 2 predominant patterns. The more dramatic and, fortunately, less common presentation is sudden onset with rapidly progressive manifestations of shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness often resulting in progression to coma or death within 24 hr. More often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or gastrointestinal symptoms, followed by non-specific signs of CNS infection, such as increasing lethargy and irritability.

The signs and symptoms of meningitis are related to the nonspecific findings associated with a systemic infection and to manifestations of meningeal irritation. Nonspecific findings include fever, anorexia and poor feeding, headache, symptoms of upper respiratory tract infection, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. Meningeal irritation is manifested as nuchal rigidity, back pain, Kernig sign (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and Brudzinski sign (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12-18 mo, Kernig and Brudzinski signs are not consistently present. Indeed fever, headache, and nuchal rigidity are present in only 40% of adults with bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanel or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens nerve paralysis, hypertension with bradycardia, apnea or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is uncommon in uncomplicated meningitis and should suggest a more chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion. Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also be the result of focal inflammation. Overall, approximately 10-20% of children with bacterial meningitis have focal neurologic signs.

**Seizures** (focal or generalized) caused by cerebrospinal fluid infection, or electrolyte disturbances occur in 20-30% of patients with meningitis. Seizures that occur on presentation or within the 1st 4 days of onset are usually of no prognostic significance. Seizures that persist after the 4th day of illness and those that are difficult to treat may be associated with a poor prognosis.

**ALTERATIONS OF MENTAL STATUS** are common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis. Additional manifestations of meningitis include photophobia and tache cébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 sec.

**DIAGNOSIS**
The diagnosis of acute pyogenic meningitis is confirmed by analysis of the CSF, which typically reveals microorganisms on Gram stain and culture, a neutrophilic pleocytosis, elevated protein, and reduced glucose concentrations (see Table 603-1). LP should be performed when bacterial meningitis is suspected. **Contraindications** for an immediate LP include (1) evidence of increased ICP (other than a bulging fontanel), such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or hypertension and bradycardia with respiratory abnormalities (see Chapter 590); (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; and (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP. If an LP is delayed, empirical antibiotic therapy should be initiated. CT scanning for evidence of a brain abscess or increased ICP should not delay therapy. LP may be performed after increased ICP has been treated or a brain abscess has been excluded.

Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80-90% of cases of meningitis. Elevations of the C-reactive protein, erythrocyte sedimentation rate, and procalcitonin have been used to differentiate bacterial (usually elevated) from viral causes of meningitis.

**Lumbar Puncture**

See Chapter 590.

The CSF leukocyte count in bacterial meningitis usually is elevated to >1,000/mm³ and, typically, there is a neutrophilic predominance (75-95%). 'Turbid CSF is present when the CSF leukocyte count exceeds 200-400/mm³. Normal healthy neonates may have as many as 30 leukocytes/mm³ (usually <10), but older children without viral or bacterial meningitis have <5 leukocytes/mm³ in the CSF; in both age groups there is a predominance of lymphocytes or monocytes. A CSF leukocyte count <250/mm³ may be present in as many as 20% of patients with acute bacterial meningitis; pleocytosis may be absent in patients with severe overwhelming sepsis and meningitis and is a poor prognostic sign. Pleocytosis with a lymphocyte predominance may be present during the early stage of acute bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8-24 hr of the initial LP. The Gram stain is positive in 70-90% of patients with untreated bacterial meningitis.

A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children already receiving antibiotic (usually oral) therapy. This is an important issue, because 25-50% of children being evaluated for bacterial meningitis are receiving oral antibiotics when their CSF is obtained. CSF obtained from children with bacterial meningitis, after the initiation of antibiotics, may be negative on Gram stain and culture. Pleocytosis with a predominance of neutrophils, elevated protein level, and a reduced concentration of CSF glucose usually persist for several days after the administration of appropriate intravenous antibiotics. Therefore, despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made. Some clinicians test CSF for the presence of bacterial antigens if the child has been pretreated with antibiotics and the diagnosis of bacterial meningitis is in doubt. These tests have technical limitations. Polymerase chain reactions using broad-based bacterial 16S ribosomal RNA gene patterns may be useful in diagnosing the
cause of culture-negative meningitis because of prior antibiotic therapy or the presence of a nonculturable fastidious pathogen.

A traumatic LP may complicate the diagnosis of meningitis. Repeat LP at a higher interspace may produce less hemorrhagic fluid, but this fluid usually also contains red blood cells. Interpretation of CSF leukocytes and protein concentration are affected by LPs that are traumatic, although the Gram stain, culture, and glucose level may not be influenced. Although methods for correcting for the presence of red blood cells have been proposed, it is prudent to rely on the bacteriologic results rather than attempt to interpret the CSF leukocyte and protein results of a traumatic LP. Children with seizure, particularly those with fever associated status epilepticus do not have a CSF pleocytosis in the absence of CNS infection or inflammatory disease.

**Differential Diagnosis**

In addition to *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b, many other microorganisms can cause generalized infection of the CNS with similar clinical manifestations. These organisms include less-typical bacteria, such as *Mycobacterium tuberculosis*, *Nocardia* spp., *Treponema pallidum* (syphilis), and *Borreella burgdorferi* (Lyme disease); fungi, such as those endemic to specific geographic areas (*Coccidioides*, *Histoplasma*, and *Blastomyces*) and those responsible for infections in compromised hosts (*Candida*, *Cryptococcus*, and *Aspergillus*); parasites, such as *Toxoplasma gondii* and those that cause cystercerosis and, most frequently, viruses (see Chapter 603.2, Table 603-2). Focal infections of the CNS including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess) may also be confused with meningitis. In addition, noninfectious illnesses can cause generalized inflammation of the CNS. Relative to infections, these disorders are uncommon and include malignancy, collagen vascular syndromes, and exposure to toxins (Table 603-2).

Determining the specific cause of CNS infection is facilitated by careful examination of the CSF with specific stains (Kinyoun carbol fuchsin for mycobacteria, India ink for fungi), cytology, antigen detection (*Cryptococcus*, serology (syphilis, West Nile virus, arboviruses), viral culture (enterovirus), and polymerase chain reaction (herpes simplex, enterovirus, and others). Other potentially valuable diagnostic tests include blood cultures, CT or MRI of the brain, serologic tests, and, rarely, meningeal or brain biopsy. A unique MRI finding in patients suspected of CNS infection is pachymeningitis (Fig. 603-1). In addition to bacterial, tuberculous, or fungal infection (Fig. 603-1), the differential diagnosis also includes immune or inflammatory diseases such as Sweet syndrome, CNs vasculitis, sarcoidosis, lymphoma, and neonatal-onset multisystem inflammatory disease.

Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis (see Tables 603-2 and 603-3). Although, in general, children with viral meningoencephalitis appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity. Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial vs viral infection tend to be distinct (see Table 603-1), specific test results may have considerable overlap.

**TREATMENT**

The therapeutic approach to patients with presumed bacterial meningitis depends on the nature of the initial manifestations of the illness. A child with rapidly progressing disease of less than 24 hr duration, in the absence of increased ICP, should receive antibiotics as soon as possible after an LP is performed. If there are signs of increased ICP or focal neurologic findings, antibiotics should be given without performing an LP and before obtaining a CT scan. Increased ICP should be treated simultaneously (see Chapter 68). Immediate treatment of associated multiple organ system failure, shock (see Chapter 70), and acute respiratory distress syndrome (see Chapter 71) is also indicated.

Patients who have a more protracted subacute course and become ill over a 4-7 day period should also be evaluated for signs of increased ICP and focal neurologic deficits. Unilateral headache, papilledema, and other signs of increased ICP suggest a focal lesion, such as a brain or epidural abscess, or subdural empyema. Under these circumstances, antibiotic therapy should be initiated before LP and CT scanning. If signs of increased ICP and/or focal neurologic signs are present, CT scanning should be performed first to determine the safety of performing an LP.

**Initial Antibiotic Therapy**

The initial (empirical) choice of therapy for meningitis in immunocompetent infants and children is primarily influenced by the antibiotic susceptibilities (Table 603-4) of *S. pneumoniae*. Selected antibiotics should achieve bactericidal levels in the CSF. Although there are substantial geographic differences in the frequency of resistance of *S. pneumoniae* to antibiotics, rates are increasing throughout the world. In the United States, 25-50% of strains of *S. pneumoniae* are currently resistant to penicillin; relative resistance (minimal inhibitory concentration of 0.1-1.0 µg/mL) is more common than high-level resistance (minimal inhibitory concentration = 2.0 µg/mL). Resistance to cefotaxime and ceftriaxone is also evident in up to 25% of isolates. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30-40% of isolates of *H. influenzae* type b produce β-lactamases and, therefore, are resistant to ampicillin. These β-lactamase–producing strains are sensitive to the extended-spectrum cephalosporins.

Based on the substantial rate of resistance of *S. pneumoniae* to β-lactam drugs, vancomycin (60 mg/kg/24 hr, given every 6 hr) is recommended as part of initial empirical therapy. Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b, cefotaxime (300 mg/kg/24 hr, given every 6 hr) or ceftriaxone (100 mg/kg/24 hr administered once per day or 50 mg/kg/dose, given every 12 hr) should also be used in initial empirical therapy. Patients allergic to β-lactam antibiotics and >1 mo of age can be treated with chloramphenicol, 100 mg/kg/24 hr, given every 6 hr. Another option for patients with allergy to β-lactam antibiotics is a combination of vancomycin and rifampin. Alternatively, patients can be desensitized to the antibiotic (see Chapter 152).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (200 mg/kg/24 hr, given every 6 hr) also should also be given because cephalosporins are inactive against *L. monocytogenes*. Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for *L. monocytogenes*. If a patient is immunocompromised and Gram-negative bacterial meningitis is suspected, initial therapy might include cefazidime and an aminoglycoside or meropenem.

**DURATION OF ANTIBIOTIC THERAPY**

Therapy for uncomplicated penicillin-sensitive *S. pneumoniae* meningitis should be for 10-14 days with a third-generation cephalosporin or intravenous penicillin (400,000 units/kg/24 hr, given every 4-6 hr). If the isolate is resistant to penicillin and the third-generation cephalosporin, therapy should be completed with vancomycin. Intravenous penicillin (300,000 units/kg/24 hr) for 5-7 days is the treatment of choice for uncomplicated *N. meningitidis* meningitis. Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days. Patients who receive intravenous or oral antibiotics before LP and who do not have an identifiable pathogen, but do have evidence of an acute bacterial infection on the basis of their CSF profile, should continue to receive therapy with ceftriaxone or cefotaxime for 7-10 days. If focal signs are present or the child does not respond to treatment, a para-meningeal focus may be present and a CT or MRI scan should be performed.

A routine repeat LP is not indicated in all patients with uncomplicated meningitis caused by antibiotic-sensitive *S. pneumoniae*, *N. meningitidis*, or *H. influenzae* type b. Repeat examination of CSF is indicated in some neonates, in all patients with Gram-negative bacillary meningitis, or in infection caused by a β-lactam–resistant *S. pneumoniae*. The CSF should be sterile within 24-48 hr of initiation of appropriate antibiotic therapy.
<table>
<thead>
<tr>
<th>Table 603-2</th>
<th>Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis</th>
</tr>
</thead>
</table>
| **VIRUSES** | Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)  
Arboviruses: Eastern equine, Western equine, Venezuelan equine,  
St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever  
Parechoivirus  
Herpes simplex (types 1, 2)  
Human herpesvirus type 6  
Varicella-zoster virus  
Epstein-Barr virus  
Parovirus B19  
Cytomegalovirus  
Adenovirus  
Variola (smallpox)  
Measles  
Mumps  
Rubella  
Influenza A and B  
Parainfluenza  
Rhinovirus  
Rabies  
Lymphocytic choriomeningitis  
Rotaviruses  
Coronaviruses  
Human immunodeficiency virus type 1 |
| **BACTERIA** | Mycobacterium tuberculosis (early and late)  
Leptospira species (leptospirosis)  
Treponema pallidum (syphilis)  
Borrelia species (relapsing fever)  
Borrelia burgdorferi (Lyme disease)  
Nocardia species (nocardioides)  
Brucella species  
Bartonella species (cat-scratch disease)  
Rickettsia rickettsii (Rocky Mountain spotted fever)  
Rickettsia prowazekii (typhus)  
Ehrlichia canis  
Coxiella burnetii  
Mycoplasma pneumoniae  
Mycoplasma hominis  
Chlamydia trachomatis  
Chlamydia psittaci  
Chlamydia pneumoniae  
Partially treated bacterial meningitis |
| **BACTERIAL PARAMENINGEAL FOCUS** | Sinusitis  
Mastoiditis  
Brain abscess  
Subdural-epidural empyema  
Craniol osteomyelitis |
| **FUNGI** | Coccidioides immitis (coccidioidomycosis)  
Blastomyces dermatitidis (blastomycosis)  
Cryptococcus neoformans (cryptococcosis)  
Histoplasma capsulatum (histoplasmosis)  
Candida species  
Other fungi (Alternaria, Aspergillus, Cephalosporium, Cladosporium,  
Drechslera hawaiensis, Paracoccidioides brasiliensis, Petriellidium boydii,  
Sporothrichum schenckii, Ustilago spp., Zygomycetes) |
| **PARASITES (NONSESINOPHILIC)** | Toxoplasma gondii (toxoplasmosis)  
Acanthamoeba spp.  
Naegelia fowleri  
Malaria |
| **POSTINFECTIOUS** | Vaccines: rabies, influenza, measles, poliovirus  
Demyelinating or allergic encephalitis |
| **SYSTEMIC OR IMMUNOLOGICALLY MEDIATED** | Acute Disseminated Encephalomyelitis (ADEM)  
Autoimmune Encephalitis  
Bacterial endocarditis  
Kawasaki disease  
Systemic lupus erythematosus  
Vasculitis, including polyarteritis nodosa  
Sjögren syndrome  
Mixed connective tissue disease  
Rheumatoid arthritis  
Behçet syndrome  
Wegener granulomatosis  
Lymphomatoid granulomatosis  
Granulomatous arteritis  
Sarcoidosis  
Familial Mediterranean fever  
Vogt-Koyanagi-Harada syndrome |
| **MALIGNANCY** | Leukemia  
Lymphoma  
Metastatic carcinoma  
Central nervous system tumor (e.g., craniopharyngioma, glioma,  
eypendymoma, astrocytoma, medulloblastoma, teratoma) |
| **DRUGS** | Intrathecal infections (contrast media, serum, antibiotics,  
anineoelastic agents)  
Nonsteroidal antiinflammatory agents  
OKT3 monoclonal antibodies  
Carbamazepine  
Azathioprine  
Intravenous immune globulins  
Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine,  
ciprofloxacin, isoniazid) |
| **MISCELLANEOUS** | Heavy metal poisoning (lead, arsenic)  
Foreign bodies (shunt, reservoir)  
Subarachnoid hemorrhage  
Postictal state  
Postmigraine state  
Mollaret syndrome (recurrent)  
Intraventricular hemorrhage (neonate)  
Familial hemophagocytic syndrome  
Postneurosurgery  
Dermoid–epidermoid cyst  
Headache, neurologic deficits  
CSF lymphocytosis (syndrome of transient headache and neurologic  
deficits with cerebrospinal fluid lymphocytosis [HanDL]) |

Meningitis caused by *Escherichia coli* or *P. aeruginosa* requires therapy with a third-generation cephalosporin active against the isolate in vitro. Most isolates of *E. coli* are sensitive to cefotaxime or ceftriaxone, and most isolates of *P. aeruginosa* are sensitive to ceftazidime. Gram-negative bacillary meningitis should be treated for 3 wk or for at least 2 wk after CSF sterilization, which may occur after 2-10 days of treatment.

Side effects of antibiotic therapy of meningitis include phlebitis, drug fever, rash, emesis, oral candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis, detectable by abdominal ultrasonography. This is usually asymptomatic but may be associated with emesis and upper right quadrant pain.

**Corticosteroids**

Rapid killing of bacteria in the CSF effectively sterilizes the meningeal infection but releases toxic cell products after cell lysis (cell wall endotoxin) that precipitate the cytokine-mediated inflammatory cascade. The resultant edema formation and neutrophilic infiltration may produce additional neurologic injury with worsening of CNS signs and symptoms. Therefore, agents that limit production of inflammatory mediators may be of benefit to patients with bacterial meningitis.

Data support the use of intravenous dexamethasone, 0.15 mg/kg/dose given every 6 hr for 2 days, in the treatment of children older than 6 wk with acute bacterial meningitis caused by *H. influenzae* type b. Among children with meningitis caused by *H. influenzae* type b, corticosteroid recipients have a shorter duration of fever, lower CSF protein and lactate levels, and a reduction in sensorineural hearing loss. Data in children regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria are inconclusive. Early steroid treatment of adults with bacterial meningitis, especially those with pneumococcal meningitis, results in improved outcome.

Corticosteroids appear to have maximum benefit if given 1-2 hr before antibiotics are initiated. They also may be effective if given concurrently with or soon after the first dose of antibiotics. Complications of corticosteroids include gastrointestinal bleeding, hypertension, hyperglycemia, leukocytosis, and rebound fever after the last dose.

**Supportive Care**

Repeated medical and neurologic assessments of patients with bacterial meningitis are essential to identify early signs of cardiovascular, CNS, and metabolic complications. Pulse rate, blood pressure, and respiratory rate should be monitored frequently. Neurologic assessment, including pupillary reflexes, level of consciousness, motor strength, cranial nerve signs, and evaluation for seizures, should be made frequently in the 1st 72 hr, when the risk of neurologic complications is greatest. Important laboratory studies include an assessment of blood urea nitrogen; serum sodium, chloride, potassium, and bicarbonate levels; urine output and specific gravity; complete blood and platelet counts; and, in the presence of petechiae, purpura, or abnormal bleeding, measures of coagulation function (fibrinogen, prothrombin, and partial thromboplastin times).

Patients should initially receive nothing by mouth. If a patient is judged to be normovolemic, with normal blood pressure, intravenous fluid administration should be restricted to one-half to two-thirds of maintenance, or 800-1,000 mL/m²/24 hr, until it can be established that increased ICP or SIADH is not present. Fluid administration may be returned to normal (1,500-1,700 mL/m²/24 hr) when serum sodium levels are normal. Fluid restriction is not appropriate in the presence of systemic hypotension because reduced blood pressure may result in reduced cerebral perfusion pressure and CNS ischemia. Therefore, shock must be treated aggressively to prevent brain and other organ dysfunction (acute tubular necrosis, acute respiratory distress syndrome). Patients with shock, a markedly elevated ICP, coma, and refractory seizures require intensive monitoring with central arterial and venous access and frequent vital sign assessments, necessitating admission to a pediatric intensive care unit. Patients with septic shock may require fluid resuscitation and therapy with vasoactive agents such as dopamine and epinephrine. The goal of such therapy in patients with meningitis is to avoid excessive increases in ICP without compromising blood flow and oxygen delivery to vital organs.

Neurologic complications include increased ICP with subsequent herniation, seizures, and an enlarging head circumference because of a subdural effusion or hydrocephalus. Signs of increased ICP should be treated emergently with endotracheal intubation and hyperventilation (to maintain the pCO₂ at approximately 25 mm Hg). In addition, intravenous furosemide (Lasix, 1 mg/kg) and mannitol (0.5-1.0 g/kg) osmotherapy may reduce ICP (see Chapter 68). Furosemide reduces brain swelling by venodilation and diuresis without increasing intracranial blood volume, whereas mannitol produces an osmolar gradient between the brain and plasma, thus shifting fluid from the CNS to the plasma, with subsequent excretion during an osmotic diuresis. Another approach to treating reductions of cerebral perfusion pressure caused by elevations of intracranial pressure is to increase systemic blood flow...
pressure using fluids (normal saline) and vasopressor agents (dopamine, norepinephrine). This method reduces the risk of systemic hypotension and may improve survival and reduce disability.

Seizures are common during the course of bacterial meningitis. Immediate therapy for seizures includes intravenous diazepam (0.1–0.2 mg/kg/dose) or lorazepam (0.05–0.10 mg/kg/dose), and careful attention paid to the risk of respiratory suppression. Serum glucose, calcium, and sodium levels should be monitored. After immediate management of seizures, patients should receive phenytoin (15–20 mg/kg loading dose, 5 mg/kg/24 hr maintenance) to reduce the likelihood of recurrence. Phenytoin is preferred to phenobarbital because it produces less CNS depression and permits assessment of a patient’s level of consciousness. Serum phenytoin levels should be monitored to maintain them in the therapeutic range (10–20 μg/mL).

### COMPLICATIONS

During the treatment of meningitis, acute CNS complications can include seizures, increased ICP, cranial nerve palsies, stroke, and meningitic encephalopathy of infancy; retinomeningoencephalitis with papilledema and retinal hemorrhage; recurrent encephalomyelitis (? allergic or autoimmune); pseudotumor cerebri; and epidemic neuromyasthenia (Iceland disease).

An encephalitic clinical pattern may follow ingestion or absorption of a number of known and unknown toxic substances; these include ingestion of lead and mercury, and percutaneous absorption of hexachlorophene as a skin disinfectant and gamma benzene hexachloride as a scabicide.

### Table 603-3 Classification of Encephalitis by Cause and Source

<table>
<thead>
<tr>
<th>I. INFECTIONS: VIRAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Spread: person to person only</td>
</tr>
<tr>
<td>1. Mumps: frequent in an unimmunized population; often mild</td>
</tr>
<tr>
<td>2. Measles: may have serious sequelae</td>
</tr>
<tr>
<td>3. Enteroviruses: frequent at all ages; more serious in newborns</td>
</tr>
<tr>
<td>4. Parechovirus</td>
</tr>
<tr>
<td>5. Rubella: uncommon; sequelae rare except in congenital rubella</td>
</tr>
<tr>
<td>6. Herpesvirus group</td>
</tr>
<tr>
<td>a. Herpes simplex (types 1 and 2, possibly 6); relatively common; sequelae frequent; devastating in newborns</td>
</tr>
<tr>
<td>b. Varicella-zoster virus: uncommon; serious sequelae not rare</td>
</tr>
<tr>
<td>c. Cytomegalovirus, congenital or acquired: may have delayed sequelae in congenital type</td>
</tr>
<tr>
<td>d. Epstein-Barr virus (infectious mononucleosis): not common</td>
</tr>
<tr>
<td>7. Pox group</td>
</tr>
<tr>
<td>a. Vaccinia and variola: uncommon, but serious CNS damage occurs</td>
</tr>
<tr>
<td>8. Parvovirus (erythema infectiosum): not common</td>
</tr>
<tr>
<td>9. Influenzas A and B</td>
</tr>
<tr>
<td>10. Adenovirus</td>
</tr>
<tr>
<td>11. Other enteroviruses, respiratory syncytial, parainfluenza, hepatitis B</td>
</tr>
<tr>
<td>B. Arthropod-borne agents</td>
</tr>
<tr>
<td>C. Arboviruses: spread to humans by mosquitoes or ticks; seasonal epidemics depend on ecology of the insect vector; the following occur in the United States:</td>
</tr>
<tr>
<td>Eastern equine California</td>
</tr>
<tr>
<td>Western equine Powassan</td>
</tr>
<tr>
<td>Venezuelan equine Dengue</td>
</tr>
<tr>
<td>St. Louis Colorado tick fever</td>
</tr>
<tr>
<td>West Nile</td>
</tr>
<tr>
<td>D. Spread by warm-blooded mammals</td>
</tr>
<tr>
<td>1. Rabies: saliva of many domestic and wild mammalian species</td>
</tr>
<tr>
<td>2. Herpesvirus simiae (“B” virus): monkeys’ saliva</td>
</tr>
<tr>
<td>3. Lymphocytic choriomeningitis: rodents’ excreta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. INFECTIONS: NONVIRAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Rickettsial: in Rocky Mountain spotted fever and typhus; encephalitic component from cerebral vasculitis</td>
</tr>
<tr>
<td>B. Mycoplasma pneumoniae: interval of some days between respiratory and CNS symptoms</td>
</tr>
<tr>
<td>C. Bacterial: tuberculous and other bacterial meningitis; often has encephalitic component</td>
</tr>
<tr>
<td>D. Spirochetal: syphilis, congenital or acquired; leptospirosis; Lyme disease</td>
</tr>
<tr>
<td>E. Cat-scratch disease</td>
</tr>
<tr>
<td>F. Fungal: immunologically compromised patients at special risk: cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; candidosis; coccidioidomycosis</td>
</tr>
<tr>
<td>G. Protozoal: Plasmodium, Trypanosoma, Naegleria, and Acanthamoeba spp.; Toxoplasma gondii</td>
</tr>
<tr>
<td>H. Metazoal: trichinosis; echinococcosis; cysticercosis; schistosomiasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. PARAINFECTION: POSTINFECTION, ALLERGIC, AUTOIMMUNE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in whom an infectious agent or 1 of its components plays a contributory role in etiology, but the intact infectious agent is not isolated in vitro from the nervous system; it is postulated that in this group, the influence of cell-mediated antigen–antibody complexes plus complement is especially important in producing the observed tissue damage</td>
</tr>
<tr>
<td>A. Associated with specific diseases (these agents may also cause direct CNS damage; see I and II)</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Rickettsial infections</td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>Influenzas A and B</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Varicella-zoster</td>
</tr>
<tr>
<td>M. pneumoniae</td>
</tr>
<tr>
<td>B. Associated with vaccines</td>
</tr>
<tr>
<td>Rabies</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Vaccinia</td>
</tr>
<tr>
<td>Yellow fever</td>
</tr>
<tr>
<td>C. Autoimmune encephalitis</td>
</tr>
<tr>
<td>D. Acute disseminated encephalomyelitis (ADEM)</td>
</tr>
<tr>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. HUMAN SLOW-VIRUS DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accumulating evidence that viruses frequently acquired earlier in life, not necessarily with detectable acute illness, participate in later chronic neurologic disease (similar events also known to occur in animals)</td>
</tr>
<tr>
<td>A. Subacute sclerosing panencephalitis; measles; rubella?</td>
</tr>
<tr>
<td>B. Creutzfeldt-Jakob disease (spongiform encephalopathy)</td>
</tr>
<tr>
<td>C. Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>D. Kuru (Fore tribe in New Guinea only)</td>
</tr>
<tr>
<td>E. Human immunodeficiency virus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V. UNKNOWN: COMPLEX GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>This group constitutes more than two-thirds of the cases of encephalitis reported to the Centers for Disease Control and Prevention, Atlanta, Georgia; the yearly epidemic curve of these undiagnosed cases suggests that the majority are probably caused by enteroviruses and/or arboviruses. There is also a miscellaneous group that is based on clinical criteria: Reye syndrome is 1 current example; others include the extinct von Economo encephalitis (epidemic during 1918–1928); myoclonic encephalopathy of infancy; retinomeningoencephalitis with papilledema and retinal hemorrhage; recurrent encephalomyelitis (? allergic or autoimmune); pseudotumor cerebri; and epidemic neuromyasthenia (Iceland disease). An encephalitic clinical pattern may follow ingestion or absorption of a number of known and unknown toxic substances; these include ingestion of lead and mercury, and percutaneous absorption of hexachlorophene as a skin disinfectant and gamma benzene hexachloride as a scabicide.</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

cerebral or cerebellar herniation, and thrombosis of the dural venous sinuses.

Collections of fluid in the subdural space develop in 10-30% of patients with meningitis and are asymptomatic in 85-90% of patients. **Subdural effusions** are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, and abnormal results of cranial transillumination. CT or MRI scanning confirms the presence of a subdural effusion. In the presence of increased ICP or a depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel (see Chapters 68 and 590). Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hypotensive seizures (see Chapter 55).

Fever associated with bacterial meningitis usually resolves within 5-7 days of the onset of therapy. **Prolonged fever** (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually caused by intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. Secondary fever refers to the recrudescence of elevated temperature after an afebrile interval. Nosocomial infections are especially important to consider in the evaluation of these patients. Pericarditis or arthritis may occur in patients being treated for meningitis, especially that caused by N. meningitidis. Involvement of these sites may result either from bacterial dissemination or from immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than does immune-mediated disease.

Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is noted most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; the coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.

### PROGNOSIS

Appropriate antibiotic therapy and supportive care have reduced the mortality of bacterial meningitis after the neonatal period to <10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10-20% of patients recovering from bacterial meningitis, and as many as 50% have some, albeit subtle, neurobehavioral morbidity. The prognosis is poorest among infants younger than 6 mo and in those with high concentrations of bacteria/bacterial products in their CSF. Those with seizures occurring more than 4 days into therapy or with coma or focal neurologic signs on presentation have an increased risk of long-term sequelae. There does not appear to be a correlation between duration of symptoms before diagnosis of meningitis and outcome.

The most common neurologic sequelae include hearing loss, cognitive impairment, recurrent seizures, delay in acquisition of language, visual impairment, and behavioral problems. **Sensorineural hearing loss** is the most common sequel of bacterial meningitis and, usually, is already present at the time of initial presentation. It is a result of cochlear infection and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal, and 5-20% of those with H. influenzae type b meningitis. Hearing loss may also be caused by direct inflammation of the auditory nerve. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment on an outpatient basis is indicated for patients who have a hearing deficit.

### PREVENTION

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent the 2 available means of reducing the likelihood of bacterial meningitis. The availability and application of each of these approaches depend on the specific infecting bacteria.

**Neisseria meningitidis**

Chromoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis regardless of age or immunization status. Close contacts should be treated with rifampin 10 mg/kg/dose every 12 hr (maximum dose of 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Close contacts include household, daycare center, and nursery school contacts, and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation). Exposed contacts should be treated immediately on suspicion of

### Table 603-4 Antibiotics Used for the Treatment of Bacterial Meningitis

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>0-7 DAYS</th>
<th>8-28 DAYS</th>
<th>INFANTS AND CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin†‡</td>
<td>15-20 divided q12h</td>
<td>30 divided q8h</td>
<td>20-30 divided q8h</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>150 divided q8h</td>
<td>200 divided q6h or q8h</td>
<td>300 divided q6h</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>100-150 divided q8h or q12h</td>
<td>150-200 divided q6h or q8h</td>
<td>225-300 divided q6h or q8h</td>
</tr>
<tr>
<td>Ceftriaxone§</td>
<td>—</td>
<td>—</td>
<td>100 divided q12h or q24h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100-150 divided q8h or q12h</td>
<td>150 divided q8h</td>
<td>150 divided q8h</td>
</tr>
<tr>
<td>Gentamicin†</td>
<td>5 divided q12h</td>
<td>7.5 divided q8h</td>
<td>7.5 divided q8h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>—</td>
<td>—</td>
<td>120 divided q8h</td>
</tr>
<tr>
<td>Nafcilin</td>
<td>75 divided q8h or q12h</td>
<td>100-150 divided q6h or q8h</td>
<td>200 divided q6h</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>150,000 divided q8h or q12h</td>
<td>200,000 divided q6h or q8h</td>
<td>300,000 divided q4h or q8h</td>
</tr>
<tr>
<td>Rifampin</td>
<td>—</td>
<td>10-20 divided q12h</td>
<td>10-20 divided q12h or q24h</td>
</tr>
<tr>
<td>Tobramycin†‡</td>
<td>5 divided q12h</td>
<td>7.5 divided q8h</td>
<td>7.5 divided q8h</td>
</tr>
<tr>
<td>Vancomycin§</td>
<td>20-30 divided q8h or q12h</td>
<td>30-45 divided q6h or q8h</td>
<td>60 divided q6h</td>
</tr>
</tbody>
</table>

*Dosages in mg/kg (units/kg for penicillin G) per day.
†Smaller doses and longer dosing intervals, especially for aminoglycosides and vancomycin for very-low-birthweight neonates, may be advisable.
‡Monitoring of serum levels is recommended to ensure safe and therapeutic values.
§Use in neonates is not recommended because of inadequate experience in neonatal meningitis.

infection in the index patient; bacteriologic confirmation of infection should not be awaited. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Two quadrivalent (A, C, Y, W-135), conjugated vaccines (MCV-4; Menactra and Menevo) are licensed by the FDA. The Advisory Committee on Immunization Practices (ACIP) to the CDC recommends routine administration of this vaccine to 11–12 yr old adolescents. Menactra is licensed for use in infants older than 9 mo of age, and Menevo for use in children older than 2 yr of age. There is also a bivalent meningococcal polysaccharide protein conjugate vaccine that provides protection against serogroups C and Y along with *H. influenzae* type b. This vaccine is licensed for use in children ages 6 wk through 18 mo. High-risk patients include those with anatomic or functional asplenia or deficiencies of terminal complement proteins. Use of meningococcal vaccine should be considered for college freshmen, especially those who live in dormitories, because of an observed increased risk of invasive meningococcal infections compared to the risk in non–college-attending, age-matched controls.

**Haemophilus influenzae** Type B

Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by *H. influenzae* type b, if any close family member younger than 48 mo has not been fully immunized or if an immunocompromised person, of any age, resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hr with the index case for at least 5 of the 7 days preceding the patient’s hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case because >50% of secondary family cases occur in the 1st wk after the index patient has been hospitalized.

The dose of rifampin is 20 mg/kg/24 hr (maximum dose of 600 mg) given once each day for 4 days. Rifampin colors the urine and perspiration red-orange, stains contact lenses, and reduces the serum concentrations of some drugs, including oral contraceptives. Rifampin is contraindicated during pregnancy.

The most striking advance in the prevention of childhood bacterial meningitis followed the development and licensure of conjugated vaccines against *H. influenzae* type b. Three conjugate vaccines are licensed in the United States. Although each vaccine elicits different profiles of antibody response in infants immunized at 2-6 mo of age, all result in protective levels of antibody with an efficacy rate against invasive infections after primary series at 93%. Efficacy is not as consistent in vitro in the case because >50% of secondary family cases occur in the 1st wk after the index patient has been hospitalized.

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**Streptococcus pneumoniae**

Routine administration of conjugate vaccine against *S. pneumoniae* is recommended for children younger than 5 yr of age. The initial dose is given at about 2 mo of age. Children who are at high risk of invasive pneumococcal infections, including those with functional or anatomic asplenia and those with underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should also receive the vaccine.

**ETIOLOGY**

**Enteroviruses** are the most common cause of viral meningoencephalitis. As of 2014, more than 70 serotypes of these small RNA viruses have been identified. The severity of infection caused by enteroviruses ranges from mild, self-limited illness with primarily meningeal involvement to severe encephalitis resulting in death or significant sequelae. Human enterovirus 68 has been associated with neurologic symptoms including flaccid paralysis. **Parechoviruses** may be an important cause of aseptic meningitis or encephalitis in infants. The clinical manifestations are similar to that of the enteroviruses with the exception of more severe MRI lesions of the cerebral cortex and at times an absence of a CSF pleocytosis.

**Arboviruses** are arthropod-borne agents, responsible for some cases of meningoencephalitis during summer months. Mosquitoes and ticks are the most common vectors, spreading disease to humans and other vertebrates, such as horses, after biting infected birds or small animals. Encephalitis in horses (“blind staggers”) may be the first indication of an incipient epidemic. Although rural exposure is most common, urban and suburban outbreaks also are frequent. The most common arboviruses responsible for CNS infection in the United States are West Nile virus (WNV), La Crosse, Powassan, and St. Louis encephalitis viruses (see Chapter 267). WNV made its appearance in the Western hemisphere in 1999. It has gradually made its way from the east to the west coast over successive summers. Cumulatively, from 1999 through 2008, a total of 47 states reported roughly 30,000 human infections caused by WNV. WNV may also be transmitted by blood transfusion, organ transplantation, or vertically across the placenta. Most children with WNV are either asymptomatic or have a nonspecific viral-like illness. Approximately 1% develop CNS disease; adults are more severely affected than children.

Several members of the *herpes family* of viruses can cause meningencephalitis. Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults. Brain involvement usually is focal; progression to coma and death occurs in 70% of cases without antiviral therapy. Severe encephalitis with diffuse brain involvement is caused by HSV type 2 in neonates who usually contract the virus from their mothers at delivery. A mild transient form of meningencephalitis may accompany genital herpes infection in sexually active adolescents; most of these infections are caused by HSV type 2. Varicella-zoster virus may cause CNS infection in close temporal relationship with chickenpox. The most common manifestation of CNS involvement is cerebellar ataxia, and the most severe is acute encephalitis. After primary infection, varicella-zoster virus becomes latent in spinal and cranial nerve roots and ganglia, expressing itself later as herpes zoster, sometimes with accompanying mild meningencephalitis. Cytomegalovirus infection of the CNS may be part of congenital infection or disseminated disease in immunocompromised hosts, but it does not cause meningencephalitis in normal infants and children. Epstein-Barr virus is associated with myriad CNS syndromes (see Chapter 254). Human herpes virus 6 can cause encephalitis, especially among immunocompromised hosts.

Mumps is a common pathogen in regions where mumps vaccine is not widely used. Mumps meningoencephalitis is mild, but deafness from damage of the 8th cranial nerve may be a sequela. Meningoencephalitis is caused occasionally by respiratory viruses (adenovirus, influenza virus, parainfluenza virus), rubella, rubella, or rabies; it may follow live virus vaccinations against polio, measles, mumps, or rubella.

**EPIDEMIOLOGY**

The epidemiologic pattern of viral meningencephalitis is primarily determined by the prevalence of enteroviruses, the most common etiology. Infection with enteroviruses is spread directly from person
Bibliography


to person, with a usual incubation period of 4-6 days. Most cases in temperate climates occur in the summer and fall. Epidemiologic considerations in aseptic meningitis due to agents other than enteroviruses also include season, geography (travel), climatic conditions, animal exposures, mosquito or tick bites, and factors related to the specific pathogen.

**PATHOGENESIS AND PATHOLOGY**

Neurologic damage is caused by direct invasion and destruction of neural tissues by actively multiplying viruses or by a host reaction to viral antigens. Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered to represent predominantly “postinfectious” or an autoimmune encephalitis.

The cerebral cortex, especially the temporal lobe, is often severely affected by HSV; the arboviruses tend to affect the entire brain; rabies has a predilection for the basal structures. Involvement of the spinal cord, nerve roots, and peripheral nerves is variable.

**CLINICAL MANIFESTATIONS**

The progression and severity of disease are determined by the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course resulting from infection with the same pathogen varies widely. Some children may appear to be mildly affected initially, only to lapse into coma and die suddenly. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations alternating with brief periods of clarity, followed by complete recovery.

The onset of illness is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days’ duration. The presenting manifestations in older children are headache and hyperesthesia, and in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. As body temperature increases, there may be mental dullness, progressing to stupor in combination with bizarre movements and convulsions. Focal neurologic signs may be stationary, progressive, or fluctuating. WNV and nonpolio enteroviruses may cause anterior horn cell injury and a flaccid paralysis. For those reported with WNV, encephalitis is more common than asptic meningitis; acute flaccid paralysis may be noted in approximately 5% of patients. Nonetheless, many patients have a nonspecific febrile illness “West Nile fever” and may never seek medical attention. Loss of bowel and bladder control and unprovoked emotional outbursts may occur.

Exanthems often precede or accompany the CNS signs, especially with echoviruses, coxsackieviruses, varicella-zoster virus, measles, rubella, and, occasionally, WNV. Examination often reveals mucal rigidity without significant localizing neurologic changes, at least at the onset.

Specific forms or complicating manifestations of CNS viral infection include Guillain-Barré syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.

**DIAGNOSIS**

The diagnosis of viral encephalitis is usually made on the basis of the clinical presentation of nonspecific prodrome followed by progressive CNS symptoms. The diagnosis is supported by examination of the CSF, which usually shows a mild mononuclear predominance (see Table 603-1). Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram (EEG) and neuroimaging studies. The EEG typically shows diffuse slow-wave activity, usually without focal changes. Neuroimaging studies (CT or MRI) may show swelling of the brain parenchyma. Focal seizures or focal findings on EEG, CT, or MRI, especially involving the temporal lobes, suggest HSV encephalitis.

**Differential Diagnosis**

A number of clinical conditions that cause CNS inflammation mimic viral meningoencephalitis (see Table 603-2). The most important group of alternative infectious agents to consider is bacteria. Most children with acute bacterial meningitis appear more critically ill than those with CNS viral infection. Parameningeal bacterial infections, such as brain, abscess or subdural or epidural empyema, may have features similar to viral CNS infections. Infections caused by *M. tuberculosis*, *T. pallidum* (syphilis), *B. burgdorferi* (Lyme disease), and *Bar tonella henselae*, the bacillus associated with cat scratch disease, tend to result in indolent courses. Analysis of CSF and appropriate serologic tests are necessary to differentiate these various pathogens.

Infections caused by fungi, rickettsiae, mycoplasma, protozoa, and other parasites may also need to be included in the differential diagnosis. Consideration of these agents usually arises as a result of accompanying symptoms, geographic locality of infection, or host immune factors.

Various noninfectious disorders may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include malignancy, autoimmunity, intracranial hemorrhage, and exposure to certain drugs or toxins. Attention to history and other organ involvement usually allow elimination of these diagnostic possibilities. Autoimmune encephalitis owing to anti-N-methyl-d-aspartate receptor antibodies is an important cause of noninfectious encephalitis in children. Detection of these antibodies in the serum or CSF confirms this diagnosis. Acute disseminated encephalomyelitis may also initially be confused with encephalitis.

**Laboratory Findings**

The CSF contains from a few to several thousand cells per cubic millimeter. Early in the disease, the cells are often polymorphonuclear; later, mononuclear cells predominate. This change in cellular type is often demonstrated in CSF samples obtained as little as 8-12 hr apart. The protein concentration in CSF tends to be normal or slightly elevated, but concentrations may be very high if brain destruction is extensive, such as that accompanying HSV encephalitis. The glucose level is usually normal, although with certain viruses, for example, mumps, a substantial depression of CSF glucose concentrations may be observed. The CSF may be normal with parechovirus and in those who have encephalitis in the absence of meningeal involvement.

The success of isolating viruses from the CSF of children with viral meningoencephalitis is determined by the time in the clinical course that the specimen is obtained, the specific etiologic agent, whether the infection is a meningitic as opposed to a localized encephalitic process, and the skill of the diagnostic laboratory staff. Isolating a virus is most likely early in the illness, and the enteroviruses tend to be the easiest to isolate, although recovery of these agents from the CSF rarely exceeds 70%. To increase the likelihood of identifying the putative viral pathogen, specimens for culture should also be obtained from nasopharyngeal swabs, feces, and urine. Although isolating a virus from 1 or more of these sites does not prove causality, it is highly suggestive.

**Detection of viral DNA or RNA by polymerase chain reaction is the test of choice in the diagnosis of CNS infection caused by HSV, parechovirus and enteroviruses, respectively.** CSF serology is the diagnostic test of choice for WNV.

A serum specimen should be obtained early in the course of illness and, if viral cultures are not diagnostic, again 2-3 wk later for serologic studies. Serologic methods are not practical for diagnosing CNS infections caused by the enteroviruses because there are too many serotypes. This approach may be useful, however, in confirming that a case is caused by a known circulating serotype. Serologic tests may also be of value in determining the etiology of nonenteroviral CNS infection, such as arboviral infection.
TREATMENT

With the exception of the use of acyclovir for HSV encephalitis (see Chapter 252), treatment of viral meningoencephalitis is supportive. Treatment of mild disease may require only symptomatic relief. Headache and hyperesthesia are treated with rest, non–aspirin-containing analgesics, and a reduction in room light, noise, and visitors. Acetaminophen is recommended for fever. Opioid agents and medications to reduce nausea may be useful, but if possible, their use in children should be minimized because they may induce misleading signs and symptoms. Intravenous fluids are occasionally necessary because of poor oral intake. More-severe disease may require hospitalization and intensive care.

It is important to monitor patients with severe encephalitis closely for convulsions, cerebral edema, inadequate respiratory exchange, disturbed fluid and electrolyte balance, aspiration and asphyxia, and cardiac or respiratory arrest of central origin. In patients with evidence of increased ICP, placement of a pressure transducer in the epidural space may be indicated. The risks of cardiac and respiratory failure or arrest are high with severe disease. All fluids, electrolytes, and medications are initially given parenterally. In prolonged states of coma, parenteral alimentation is indicated. SIADH is common in acute CNS disorders; monitoring of serum sodium concentrations is required for early detection (see Chapter 559). Normal blood levels of glucose, magnesium, and calcium must be maintained to minimize the likelihood of convulsions. If cerebral edema or seizures become evident, vigorous treatment should be instituted.

PROGNOSIS

Supportive and rehabilitative efforts are very important after patients recover from the acute phase of illness. Motor incoordination, convulsive disorders, total or partial deafness, and behavioral disturbances may follow viral CNS infections. Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur. Special facilities and, at times, institutional placement may become necessary. Some sequelae of infection may be very subtle. Therefore, neurodevelopmental and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

Most children completely recover from viral infections of the CNS, although the prognosis depends on the severity of the clinical illness, the specific causative organism, and the age of the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor, with potential deficits being intellectual, motor, psychomotor, epileptic, visual, or auditory in nature. Severe sequelae should also be anticipated in those with infection caused by HSV. Although some literature suggests that infants who contract viral meningoencephalitis have a poorer long-term outcome than older children, most other data refute this observation. Approximately 10% of children younger than 2 yr of age with enteroviral CNS infections suffer an acute complication such as seizures, increased ICP, or coma. Almost all have favorable long-term neurologic outcomes.

PREVENTION

Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases in the United States. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis. Control of encephalitis caused by arboviruses has been less successful because specific vaccines for the arboviral diseases that occur in North America are not available. Control of insect vectors by suitable spraying methods and eradication of insect breeding sites, however, reduces the incidence of these infections. Furthermore, minimizing mosquito bites through the application of N,N-diethyl-3-methylbenzamide (DEET)-containing insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces the risk of arboviral infection.

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603.3 Eosinophilic Meningitis

Charles G. Prober and Nivedita S. Srinivas

Eosinophilic meningitis is defined as 10 or more eosinophils/mm³ of CSF. The most common cause worldwide of eosinophilic pleocytosis is CNS infection with helminthic parasites. In countries such as the United States, where helminthic infestation is uncommon, however, the differential diagnosis of CSF eosinophilic pleocytosis is broad.

ETIOLOGY

Although any tissue-migrating helminth may cause eosinophilic meningitis, the most common cause is human infection with the rat lungworm, Angiostrongylus cantonensis (see Chapter 297). Other parasites that can cause eosinophilic meningitis include Gnathostoma spinigerum (dog and cat roundworm) (see Chapter 297), Baylisascaris procyonis (raccoon roundworm), Ascaris lumbricoides (human roundworm), Trichinella spiralis, Toxocara canis, T. gondii, Paragonimus westermani, Echinococcus granulosus, Schistosoma japonicum, Onchocerca volvulus, and Taenia solium. Eosinophilic meningitis may also occur as an unusual manifestation of more common viral, bacterial, or fungal infections of the CNS. Noninfectious causes of eosinophilic meningitis include multiple sclerosis, malignancy, hypereosinophilic syndrome, or a reaction to medications or a ventriculoperitoneal shunt.

EPIDEMIOLOGY

A. cantonensis is found in Southeast Asia, the South Pacific, Japan, Taiwan, Egypt, Ivory Coast, and Cuba. Infection is acquired by eating raw or undercooked freshwater snails, slugs, prawns, or crabs containing infectious 3rd-stage larvae. Gnathostoma infections are found in Japan, China, India, Bangladesh, and Southeast Asia. Gnathostomiasis is acquired by eating undercooked or raw fish, frog, bird, or snake meat.

CLINICAL MANIFESTATIONS

When eosinophilic meningitis results from helminthic infestation, patients become ill 1-3 wk after exposure. This reflects the transit time for parasites to migrate from the gastrointestinal tract to the CNS. Common concomitant findings include fever, peripheral eosinophilia, vomiting, abdominal pain, creeping skin eruptions, or pleurisy. Neurologic symptoms may include headache, meningismus, ataxia, cranial nerve palsies, and paresthesias. Paraparesis or incontinence can result from radiculitis or myelitis.

DIAGNOSIS

The presumptive diagnosis of helminth-induced eosinophilic meningitis is most often based on travel and exposure history in the presence of typical clinical and laboratory findings. Direct visualization of helminths in CSF is affected by the relatively low organism burden, resulting in limited diagnostic sensitivity. Serologic assays for helminthic infections are also of limited utility because they are not readily available commercially and there is substantial cross-reactivity between different helminth species.

TREATMENT

Treatment is supportive, because infection is self-limited and anthelminthic drugs do not appear to influence the outcome of infection. Analgesics should be given for headache and radiculitis, and CSF removal or shunting should be performed to relieve hydrocephalus, if present. Steroids may decrease the duration of headaches in adults with eosinophilic meningitis.

PROGNOSIS

The prognosis is good; 70% of patients improve sufficiently to leave the hospital in 1-2 wk. Mortality associated with eosinophilic meningitis is <1%.

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Chapter 603  ◆ Central Nervous System Infections 2948.e1

Bibliography
Bibliography
Brain Abscess

Charles G. Prober and Roshni Mathew

Brain abscesses can occur in children of any age but are most common in children between 4 and 8 yr old and in neonates. The causes of brain abscess include embolization as a result of congenital heart disease with right-to-left shunts (especially tetralogy of Fallot), endocarditis, meningitis, chronic otitis media and mastoiditis, sinusitis, soft-tissue infection of the face or scalp, orbital cellulitis, dental infections, severe complicated pneumonia, penetrating head injuries, immunodeficiency states, and infection of ventriculoperitoneal shunts.

**PATHOLOGY**

Cerebral abscesses are evenly distributed between the 2 hemispheres, and 80% of cases are divided equally between the frontal, parietal, and temporal lobes. Brain abscesses in the occipital lobe, cerebellum, and brainstem account for approximately 20% of the cases. Most brain abscesses are single, but 30% are multiple and may involve more than 1 lobe. The pathogenesis is undetermined in 10-15% of cases. An abscess in the frontal lobe is often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with chronic otitis media and mastoiditis. Abscesses resulting from penetrating injuries tend to be singular and caused by *Staphylococcus aureus*, whereas those resulting from septic emboli, congenital heart disease, or meningitis often have several causal organisms.

**ETIOLOGY**

The predominant organisms causing brain abscesses in children are aerobic and anaerobic streptococci (60-70% of the cases) with *Streptococcus milleri* gp (*Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus intermedius*) being increasingly isolated from surgically drained brain abscesses. Other important streptococci include group A and B streptococci, *Streptococcus pneumoniae,* and *Enterococcus faecalis.* Other bacteria isolated from brain abscesses include anaerobic organisms (Gram-positive cocci, *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., *Actinomyces* spp.) and Gram-negative aerobic bacilli (*Haemophilus aphrophilus, Haemophilus parainfluenzae, Haemophilus influenzae, Enterobacter, Escherichia coli,* and *Proteus* spp.). *Cito-

**CLINICAL MANIFESTATIONS**

The early stages of cerebritis and abscess formation are associated with nonspecific symptoms, including low-grade fever, headache, and lethargy. The significance of these symptoms is generally not recognized, and an oral antibiotic is often prescribed with resultant transient relief. As the inflammatory process proceeds, vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma may develop. A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache. If the abscess ruptures into the ventricular cavity, overwhelming shock and death usually ensue.

**DIAGNOSIS**

The peripheral white blood cell count can be normal or elevated, and the blood culture is positive in 10% of cases. Examination of the cerebrospinal fluid shows variable results; the white blood cells and protein content may be minimally elevated or normal, and the glucose level may be low. Cerebrospinal fluid cultures are rarely positive; culture of pus from the neurosurgical drainage is the key to establishing a bacteriologic diagnosis. However, the culture can be sterile in a substantial number of cases and 16S bacterial ribosomal RNA polymerase chain reaction amplification and sequencing may be used to identify unculturable bacteria in brain abscesses. Because examination of the cerebrospinal fluid is seldom useful and a lumbar puncture may cause herniation of the cerebellar tonsils, the procedure should not be undertaken in a child suspected of having a brain abscess. The electroencephalogram shows corresponding focal slowing, and the radionuclide brain scan indicates an area of enhancement caused by disruption of the blood–brain barrier in more than 80% of cases. CT with contrast and MRI are the most reliable methods of demonstrating cerebritis and abscess formation (Fig. 604-1). MRI is the diagnostic test of choice. The CT findings of cerebritis are characterized by a parenchymal low-density lesion, and MRI T2-weighted images indicate increased signal intensity. An abscess cavity shows a ring-enhancing lesion by contrast CT, and the MRI also demonstrates an abscess capsule with gadolinium administration.

**TREATMENT**

The initial management of a brain abscess includes prompt diagnosis and institution of an antibiotic regimen that is based on the probable pathogenesis and the most likely organism. When the cause is unknown, the combination of vancomycin, a third-generation cephalosporin, and metronidazole is commonly used. The same regimen is initiated when otitis media, sinusitis, or mastoiditis is the likely cause. If there is a history of penetrating head injury, head trauma, or neurosurgery; vancomycin plus a third-generation cephalosporin is appropriate. When cyanotic congenital heart disease is the predisposing factor, ampicillin-sulbactam alone or a third-generation cephalosporin plus metronidazole may be used. Meropenem has good activity against Gram-negative bacilli, anaerobes, staphylococci, and *streptococci,*
including most antibiotic-resistant pneumococci, and may be used alone to replace the combination of metronidazole and a β-lactam in the previous regimens. Notably, meropenem does not provide activity against methicillin-resistant *S. aureus* and may have decreased activity against penicillin-resistant strains of *S. pneumoniae*, indicating that vancomycin should remain a part of the initial regimen when these organisms are suspected. Abscesses secondary to an infected ventriculoperitoneal shunt may be initially treated with vancomycin and ceftriaxone. When *Citrobacter* meningitis (often in neonates) leads to abscess formation, a third-generation cephalosporin is used, typically in combination with an aminoglycoside. *Listeria monocytogenes* may cause a brain abscess in the neonate and if suspected, ampicillin should be added to the cephalosporin. In immunocompromised patients, broad-spectrum antibiotic coverage is used, and amphotericin B therapy should be considered.

A brain abscess can be treated with antibiotics without surgery if the abscess is <2 cm in diameter, the illness is of short duration (<2 wk), there are no signs of increased intracranial pressure, and the child is neurologically intact. If the decision is made to treat with antibiotics alone, the child should have follow-up neuroimaging studies to ensure the abscess is decreasing in size. An encapsulated abscess, particularly if the lesion is causing a mass effect or increased intracranial pressure, should be treated with a combination of antibiotics and aspiration. Surgical excision of an abscess is rarely required, because the procedure may be associated with greater morbidity compared with aspiration of a cavity. Surgery is indicated when the abscess is ≥2.5 cm in diameter, gas is present in the abscess, the lesion is multiloculated, the lesion is located in the posterior fossa, or a fungus is identified. Associated infectious processes, such as mastoiditis, sinusitis, or a periorbital abscess, may require surgical drainage. The duration of antibiotic therapy depends on the organism and response to treatment but is usually 4-6 wk.

**PROGNOSIS**

Mortality rates prior to 1980s ranged from 11-53%. More recent mortality rates accompanying wider use of CT and MRI, improved microbiologic techniques and prompt antibiotic and surgical management, range from 5-10%. Factors associated with high mortality rate at the time of admission include age younger than 1 yr, multiple abscesses and coma. Long-term sequelae occur in about one-third of the survivors and include hemiparesis, seizures, hydrocephalus, cranial nerve abnormalities, and behavior and learning problems.

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Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is a clinical syndrome that mimics brain tumors and is characterized by increased intracranial pressure \( \geq 280 \text{ mm Hg} \) in sedated or obese children; \( \geq 250 \text{ mm Hg} \) in nonobese, nonsedated children with a normal cerebrospinal fluid (CSF) cell count and protein content and normal to slightly decreased ventricular size, and normal ventricular anatomy and position documented by MRI. Papilledema is universally present in children old enough to have a closed fontanel (Fig. 605-1).

**ETIOLOGY**

Table 605-1 lists the many causes of pseudotumor cerebri. There are many explanations for the development of pseudotumor cerebri, including alterations in CSF absorption and production, subtle cerebral edema, abnormalities in vasmotor control and cerebral blood flow, and venous obstruction. The causes of pseudotumor are numerous and include metabolic disorders (galactosemia, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatasia, prolonged corticosteroid therapy or rapid corticosteroid withdrawal, possibly growth hormone treatment, refeeding of a significantly malnourished child, hypervitaminosis A, severe vitamin A deficiency, Addison disease, obesity, menarche, oral contraceptives, and pregnancy), infections (roseola infantum, sinusitis, chronic otitis media and mastoiditis, Guillain-Barré syndrome), drugs (nalidixic acid, doxycycline, minocycline, tetracycline, nitrofurantoin, isotretinoin used for acne therapy especially when combined with tetracycline), hematologic disorders (polycythemia, hemolytic and iron-deficiency anemias [see Fig. 605-1],

Figure 605-1 Optic nerve photos of the right and left eyes, respectively, demonstrating grade 5 optic nerve head edema with characteristics, including (A) total obscuration of the optic cup; (B) total obscuration of a segment of a major blood vessel; (C) total obscuration of disc margin; and (D) macular star. (From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female. J Pediatr 163:1518–1519, 2013, Fig. 1.)
Table 605-1  Etiology of Childhood Pseudotumor Cerebri

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMATOLOGIC</td>
<td>Wiskott-Aldrich syndrome, Iron-deficiency anemia, Aplastic anemia, Sickle cell disease, Bone marrow transplantation and associated treatments, Prothrombotic states, Fanconi anemia</td>
</tr>
<tr>
<td>INFECTIONS</td>
<td>Acute sinusitis, Otitis media (lateral sinus thrombosis), Mastoiditis, Tonsillitis, Measles, Roseola, Varicella, recurrent varicella-zoster virus infection, Lyme disease, HIV or associated treatment complications</td>
</tr>
<tr>
<td>DRUGS</td>
<td>Tetracyclines, Sulfonamides, Salicylic acid, Fluoroquinolones, Corticosteroid therapy and withdrawal, Nitrofurantoin, Cytarabine, Cyclosporine, Phenytoin, Mesalazine, Isotretinoin, Amiodarone, 1-Deamino-8-D-arginine vasopressin (DDAVP), Lithium, Levonorgestrel implants, Oral contraceptive pills</td>
</tr>
<tr>
<td>NUTRITIONAL</td>
<td>Hypovitaminosis A, Vitamin A intoxication, Hyperalimentation in a malnourished patient, Vitamin D-dependent rickets</td>
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<td>CONNECTIVE TISSUE DISORDERS</td>
<td>Antiphospholipid antibody syndrome, Systemic lupus erythematosus, Behçet disease</td>
</tr>
<tr>
<td>OTHER</td>
<td>Dural sinus thrombosis, Obesity (in pubertal patients), Bariatric surgery, Head trauma, Superior vena cava syndrome, Arteriovenous malformation, Sleep apnea, Guillain-Barré syndrome, Cronh disease, Ulcerative colitis, Turner syndrome</td>
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<tr>
<td>POSSIBLE ASSOCIATIONS</td>
<td>Cystic fibrosis, Cystinosis, Down syndrome, Hypomagnesemia–hypercalciuria, Galactokinase deficiency, Galactosemia, Atrial septal defect repair, Moebius syndrome, Sarcoïdosis</td>
</tr>
</tbody>
</table>

When a cause is not identified, the condition is classified as idiopathic intracranial hypertension. The presence of focal neurologic signs should prompt an investigation to uncover a process other than pseudotumor cerebri. Any patient suspected of pseudotumor cerebri should undergo an MRI. MR angiography/MR venography should be considered in patients suspected of having dural sinus thrombosis.

**CLINICAL MANIFESTATIONS**

The most frequent symptom is chronic (weeks to months), progressive, frontal headache that may worsen with postural changes or a Valsalva maneuver, and although vomiting also occurs, the vomiting is rarely as persistent and insidious as that associated with a posterior fossa tumor. Transient visual obscuration lasting seconds and diplopia (secondary to dysfunction of the abducens nerve) may also occur as may pulsatile tinnitus. Most patients are alert and lack constitutional symptoms. Examination of the infant with pseudotumor cerebri characteristically reveals a bulging fontanel and a “cracked pot sound” or Macwewen sign (percussion of the skull produces a resonant sound) resulting from separation of the cranial sutures. **Papilledema** with an enlarged blind spot is the most consistent sign in a child beyond infancy. Papilledema may be absent or mild in infants with pseudotumor cerebri because high CSF pressure may be transmitted to the soft fontanels earlier than the optic nerves. Early optic nerve edema may be noted with orbit ultrasonography. Inferior nasal or peripheral visual field defects may be detected on formal tangent screen testing. The presence of focal neurologic signs should prompt an investigation to uncover a process other than pseudotumor cerebri. Any patient suspected of pseudotumor cerebri should undergo an MRI. MR angiography/MR venography should be considered in patients suspected of having dural sinus thrombosis.

**TREATMENT**

The key objective in management is recognition and treatment of the underlying cause. There are no randomized clinical trials to guide the treatment of pseudotumor cerebri. Pseudotumor cerebri can be a self-limited condition, but optic atrophy and blindness are the most significant complications of untreated pseudotumor cerebri (Fig. 605-2). The obese patient should be treated with a weight-loss regimen, and if a drug is thought to be responsible, it should be discontinued. For most patients old enough to participate in such testing, serial monitoring of visual function is required. Serial determination of visual acuity, color vision, and visual fields is critical in this disease. Serial optic nerve examination is essential as well. Optical coherence tomography is useful to serially follow changes in papilledema. Serial visual-evoked potentials are useful if the visual acuity cannot be reliably documented. The initial lumbar tap that follows a CT or MRI scan is diagnostic and may be therapeutic. The spinal needle produces a small rent in the dura that allows CSF to escape the subarachnoid space, thus reducing the intracranial pressure. Several additional lumbar taps and the removal

![Figure 605-2 Bilateral optic atrophy is evident upon resolution of the papilledema, 1 mo after bilateral optic nerve sheath fenestrations. (From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female. J Pediatr 163:1518–1519, 2013, Fig. 2.)](image-url)
of sufficient CSF to reduce the opening pressure by 50% occasionally lead to resolution of the process. Acetazolamide, 10-30 mg/kg/24 hr, is an effective regimen. Corticosteroids are not routinely administered, although they may be used in a patient with severe intracranial pressure elevation who is at risk of losing visual function and is awaiting a surgical decompression. Sinus thrombosis is typically addressed by anticoagulation therapy. Rarely, a ventriculoperitoneal shunt or subtemporal decompression is necessary, if the aforementioned approaches are unsuccessful and optic nerve atrophy supervenes. Some centers perform optic nerve sheath fenestration to prevent visual loss. Any patient whose intracranial pressure proves to be refractory to treatment warrants consideration for repeat neuroradiologic studies. A slow-growing tumor or obstruction of a venous sinus may become evident by the time of reinvestigation.

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Chapter 605  Idiopathic Intracranial Hypertension/Pseudotumor Cerebri

Bibliography

Beyond infancy the spinal cord in humans ends in the conus medullaris at about the level of L1. The position of the conus below L2 is consistent with a congenital tethered spinal cord. For normal humans as the spine flexes and extends, the spinal cord is free to move up and down within the spinal canal. If the spinal cord is fixed at any point, this movement is restricted and the spinal cord and nerve roots become stretched. This fixing of the spinal cord, regardless of the underlying cause of the fixation, is called a tethered cord. When severe pain or neurologic deterioration occurs in response to the fixation, it is called the tethered cord syndrome.

In its simplest form the tethered cord syndrome results from a thickened filum terminale, which normally extends as a thin, very mobile structure from the tip of the conus to the sacrococcygeal region where it attaches. When this structure is thickened and shortened, the conus is found to end at levels below L2. This stretching between 2 points is likely to cause symptoms later in life. Fatty infiltration is often seen in the thickened filum (Fig. 606-1).

Any condition that fixes the spinal cord can be the cause of the tethered cord syndrome. Conditions that are well established to cause symptomatic tethering include various forms of occult dysraphism such as lipomyelomeningocele, myelocystocele, and diastematomyelia. These conditions are associated with cutaneous manifestations such as midline lipomas often with asymmetry of the gluteal fold (Fig. 606-2), and hairy patches called hypertrichosis (Fig. 606-3). Probably the most common type of symptomatic tethered cord involves patients who had previously undergone closure of an open myelomeningocele and later become symptomatic with pain or neurologic deterioration. Tethered cord syndrome can also be associated with attachment of the spinal cord in patients who undergo surgical procedures that disrupt the pial surface of the spinal cord.

It is possible that a patient can be suffering from a tethered cord with the conus medullaris in a completely normal position. Although this concept remains controversial, recent reports suggest that half of children with new onset of incontinence found to be neurologic in nature by urodynamic measurements can be successfully treated by sectioning of the filum terminale in the context of normal radiology. This concept will require a randomized controlled trial to evaluate the efficacy of this approach.

**CLINICAL MANIFESTATIONS**

Patients at risk for the subsequent development of the tethered cord syndrome can often be identified at birth by the presence of an open myelomeningocele or by cutaneous manifestations of dysraphism. It is important to examine the back of the newborn for cutaneous midline lesions (lipoma, dermal sinus, tail, or hairy patch) that may signal an
Diastematomyelia

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DIAGNOSTIC EVALUATION

When patients present with symptoms related to the tethered cord syndrome, a thorough motor and sensory examination of the patient must be documented. Assessment of bladder function with an ultrasonogram of the bladder and urodynamic studies is useful in analyzing bladder innervation. MRI is the diagnostic study of choice to reflect the anatomy of the tethering lesion and to provide information about the risks of surgical intervention.

TREATMENT

There are no nonsurgical options for the management of tethered cord syndrome. Because the presence of tethering is most likely to be at least suspected in the newborn, prophylactic surgery to prevent late deterioration has been advocated by some neurosurgeons. This strategy remains controversial and depends to some extent on a careful assessment of the risks compared to the benefits. If surgical intervention is chosen, microsurgical dissection with release of the spinal cord attachment to the overlying dura is the goal of treatment.

OUTCOME

The outcome of releasing a thickened filum terminale or detethering of patients with diastematomyelia is routinely good, and the chance of recurrent symptoms is very low. Patients with symptomatic tethered cord who undergo repair of a myelomeningocele or a lipomyelomeningocele have a significant possibility of recurrent tethering and recurrent symptoms.

Bibliography is available at Expert Consult.

606.2 Diastematomyelia

Harold L. Rekate

DIASTEMATOMYELIA: SPLIT-CORD MALFORMATION

Diastematomyelia is a relatively rare form of occult dysraphism in which the spinal cord is divided into 2 halves. In type 1 split-cord malformation, there are 2 spinal cords, each in its own dural tube and separated by a spicule of bone and cartilage (Fig. 606-5A). In a type 2 split-cord malformation, the 2 spinal cords are enclosed in a single dural sac with a fibrous septum between the 2 spinal segments (Fig. 606-5B). In both cases the anatomy of the outer half of the spinal cord is essentially normal while the medial half is extremely underdeveloped. Undeveloped nerve roots and dentate ligaments terminate medially into the membranous dural tube in type 1 cases and terminate in the membranous septum in type 2 cases. Both types have an associated defect in the bony spinal segment. In the case of type 2 lesions, this defect can be quite subtle.

CLINICAL MANIFESTATIONS

Patients with both type 1 and type 2 split-cord malformations may have subtle signs of neurologic involvement such as unilateral calf atrophy and a high arch to 1 or both feet early in life, but they are more likely to be neurologically normal. These patients are tethered by the adherence of the spinal cord to the median membrane or dural sac. Later they may develop progressive loss of bowel and bladder function and sensory and motor difficulties in the lower extremities. Back pain is a common symptom in adolescents and adults with split-cord malformation but is uncommon in small children.

Cutaneous manifestations of dysraphism are present in 90% of patients with split-cord malformations. Large, hairy, midline patches called hypertrichosis, the most common cutaneous manifestations, are present in approximately 60% of the cases.

DIAGNOSTIC EVALUATION

MRI, the study of choice, shows the 2 spinal cords. The frequent association of bony abnormalities in this condition may require further evaluation with radiography or computed tomography.

TREATMENT

The treatment of split-cord malformations is surgical. This abnormality is a form of tethered cord syndrome, and its treatment is to release the spinal cord to move freely with movement of the spine. In type 1 split-cord malformations, the 2 half cords are in separate dural sacs with medial attachment to the dura and bony septum. In this case the dura needs to be opened, the bony septum removed, the medial attachments to the dura lysed, and a single dural tube created. For type 2 lesions,
Bibliography


the membranous septum should be lysed. An attachment of this membrane to the anterior dura should be explored and lysed as well. Retethering of this type is rare as there is no reason to disrupt the pial layer of the spinal cord.

Bibliography is available at Expert Consult.

606.3 Syringomyelia
Harold L. Rekate

Syringomyelia is a cystic distention of the spinal cord caused by obstruction of the flow of spinal fluid from within the spinal cord to its point of absorption. There are 3 recognized forms of syringomyelia depending on the underlying cause. Communicating syringomyelia implies that cerebrospinal fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord and is assumed to be the source of the CSF that distends the spinal cord. Noncommunicating syringomyelia implies that ventricular CSF does not communicate with the fluid within the spinal cord. It primarily occurs in the context of intramedullary tumors and obstructive lesions. In the final form of syringomyelia, that is, posttraumatic syringomyelia, spinal cord injury results in damage and subsequent softening of the spinal cord. This softening, combined with the scarring of the surrounding spinal cord tissue, results in progressive distention of the cyst. Syringomyelia has been associated with Chiari anomalies and in patients with Ehlers-Danlos syndrome; most are isolated findings unassociated with syndromes.

CLINICAL MANIFESTATIONS

Syringomyelia develop insidiously over years or decades. The classic presentation is the central cord syndrome. In this situation the patient develops numbness beginning in the shoulder in a cape-like distribution followed by the development of atrophy and weakness in the upper extremities. Trophic ulcers of the hands are characteristic of advanced cases. The central cord syndrome results from damage to the central spinal cord and the orientation of spinal tracts from proximal to distal leading to selective involvement of the upper rather than the lower extremities.

Other forms of presentation include scoliosis that may be rapidly progressive and often can be presumed from the absence of superficial abdominal reflexes. Urgency and bladder dysfunction as well as lower extremity spasticity also may be part of the presentation.

In patients with syringomyelia related to spinal cord injury, the presentation is usually severe pain in the area of the spinal cord distention above the level of the initial injury. There is also an ascending level of motor and sensory dysfunction.

DIAGNOSTIC EVALUATION

MRI is the radiologic study of choice (Figs. 606-6 and 606-7). The study should include the entire spine and should include gadolinium-enhanced sequences. Specific attention should be paid to the craniovertebral junction because of the frequent association of syringomyelia with Chiari I and II malformations. Obstruction to the flow of CSF from the fourth ventricle can cause syringomyelia; therefore, most patients also should undergo imaging of the brain.
Bibliography
TREATMENT
The treatment of syringomyelia should be tailored to the underlying cause. If that cause can be removed or ameliorated, the syrinx should improve. Traumatic syrinxes result from hematymelia in the substance of the spinal cord coupled with severe arachnoidal scarring around the circumference of the spinal cord. When progressive this form of syringomyelia is treated by exploration and lysis of the adhesions that fix the spinal cord to the overlying dura. In cases of complete spinal cord injury, as is usually found in the thoracic spinal cord, the most effective treatment is the transection of the spinal cord, which would both drain the syrinx and detether the spinal cord. Doing so drains the fluid from the spinal cord. In cases of incomplete spinal cord injury, functioning neurologic elements must be protected. Microscopic lysis of the scar surrounding the spinal cord at the point of injury allows the spinal cord to collapse and prevents it from being distorted by a hydrostatic column.

Communicating syringomyelia is most frequently seen in the context of abnormalities at the craniovertebral junction caused by inflammatory conditions such as chronic meningitis as seen in tuberculosis or meningococcal carcinomatosis. There is frequently a causative association with hindbrain herniation as in Chiari malformations (see Fig. 606-6). In such cases decompression of the craniovertebral junction is usually effective in the management of the syringomyelia. In the context of the Chiari II malformation associated with spina bifida, syringomyelia usually results from an insidious failure of the shunt used to treat the hydrocephalus. This distention of the spinal cord results in a rapid development of scoliosis and occasionally spasticity in the lower extremities. Repair of the shunt is effective treatment.

Noncommunicating syringomyelia results from blocking the flow of spinal cord extracellular fluid or CSF within the central canal by an intramedullary spinal cord tumor or severe external compression of the spinal cord. In such cases, management should be directed to tumor resection or to decompression of constricting elements.

Drainage procedures can result in symptomatic and radiographic improvement. Syrinx-to-subarachnoid shunting with a small piece of shunt tubing is 1 form of treatment. Syrinx-to-pleural or syrinx-to-peritoneal shunting is more likely to result in improvement in the radiographic appearance of the syrinx. In patients with syringomyelia that extends to the conus medullaris, remnants of the central canal can be found in the filum terminale. Lysis of this structure near the conus can provide effective drainage.

Some children who show no testable neurologic findings are being referred to pediatric neurosurgeons with the diagnosis of syringomyelia. Many of these children were scanned because of back pain or as part of a screening for scoliosis. They are found on MRI to have a persistent central canal and the diagnosis of syringomyelia is made. Some have been scanned sequentially for follow up and banned from athletic activities. These syrinxes are 1–3 mm in diameter and extend over 2 segments (see Fig. 606-7). There is no distortion of the spinal cord in the region and no change in signal of the surrounding spinal cord. These syrinxes have been called “idiopathic” syrinxes. Follow-up of significant numbers of such children has shown them to be benign in nature and probably represent a normal variant. There does not seem to be a need for routine follow-up imaging without new symptoms. They need no treatment and do not require limitations of activity.

Bibliography is available at Expert Consult.

606.4 Spinal Cord Tumors
Harold L. Rekate

Tumors of the spine and spinal cord are rare in children. Different types of tumors have different relationships with the spinal cord, meninges, and bony elements of the spine (Fig. 606-8). Intramedullary spinal cord tumors arise within the substance of the spinal cord itself (Fig. 606-9). They represent between 5% and 15% of primary central nervous system tumors. This percentage may well reflect the total volume of spinal cord as opposed to brain. Approximately 10% of intramedullary spinal cord tumors are malignant astrocytic tumors, but most are World Health Organization grade I or II tumors of glial or ependymal origin. In children, low-grade astrocytomas and gangliogliomas represent the most common tumor types with ependymomas being less common than in adults. Ependymomas in children are frequently associated with neurofibromatosis (NF-2).

Except in the context of NF-1 and NF-2, intradural extramedullary tumors are extremely rare in children. Most are nerve sheath tumors,
Bibliography
Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and interfere with normal CSF flow dynamics. Papilledema is observed in a few patients, usually in association with markedly elevated CSF protein levels that presumably interconnect with normal CSF flow dynamics. Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and present with symptoms and signs relative to the nerve root involved. Pain in a band-like distribution around the chest or into an extremity is the most common presenting complaint. Tumor growth eventually leads to spinal cord compression and involvement of adjacent nerve roots.

Tumors rarely arise in the fat of the epidural space; most epidural tumors arise in the bony compartment of the spine. They can present abruptly with severe pain and neurologic deficit at the time of pathologic fracture of the vertebral body. Benign tumors such as giant cell tumors and aneurysmal bone cysts present more insidiously as the tumor slowly grows and begins to compress neural structures.

**DIAGNOSTIC EVALUATION**

MRI with and without gadolinium enhancement of the spinal cord is the diagnostic study of choice and is essential in the diagnosis of spinal cord tumors, especially intramedullary spinal cord tumors. Most astrocytic tumors of the spinal cord and most ependymomas show diffuse enhancement and will distend the spinal cord focally. These tumors may involve the entire length of the spinal cord (holocord astrocytomas). MRI also shows the relationship between the normal spinal cord and tumor embedded within spinal cord tissue. These tumors are frequently associated with a syrinx, which is usually distal to the tumor. Nerve sheath tumors characteristically enhance and are focal. They may exit through the neural foramen and distend the canal as can be seen on MRI. They also may be visualized on plain radiographs of the affected area of the spine.

Plain radiographs of the spine are helpful in defining the relationship of extradural tumors to the bony spine and in documenting evidence of instability in the case of pathologic compression fractures. When a pathologic fracture occurs, CT is essential to determine the effect of the tumor on the bone. Because many of these tumors occur as metastatic lesions, a general staging of the extent of disease is essential. In the case of Langerhans cell histiocytosis, a thorough bone survey should be conducted to look for other lesions. Radionuclide bone scanning is also useful in determining the extent of the disease.

**TREATMENT**

The primary treatment of both intramedullary and extramedullary intradural tumors is surgical removal. For both low-grade astrocytomas and ependymomas, microsurgical removal with the intent of total removal is the treatment of choice. This goal should be attainable in all patients with ependymomas and in most patients with low-grade astrocytomas and gangliogliomas. Adjunctive treatment of these tumors is unwarranted in patients treated with adequate surgical resection. Likewise, schwannomas should be resectable. Occasionally, however, the nerve root must be resected. Doing so may be of no consequence in the thoracic spinal cord, but an attempt to remove the tumor while salvaging the motor root in the cervical and lumbar-sacral region is critical to preserve movement. Malignant astrocytic tumors cannot be resected without major morbidity and, in any case, carry an extremely poor prognosis. In the case of grades III and IV astrocytomas of the spinal cord, decompression and biopsy followed by radiation therapy and possibly chemotherapy are utilized.

The diagnosis and treatment of extramedullary spinal cord tumors must be individualized. Patients with distention of the vertebral body or with unstable pathologic fractures benefit from extensive resection of the involved vertebral bodies and will likely need fusion. For extramedullary tumors with soft-tissue components such as neuroblastomas, treatment is determined by the nature of the tumor and degree of spinal cord compression, and directed following needle biopsy of the lesion. In the absence of significant neurologic compression, surgical intervention is rarely indicated.

**OUTCOME**

The prognosis for patients with benign intramedullary spinal cord tumors depends, to some extent, on the patient’s condition at the time of surgical intervention. It is very unlikely that nonambulatory patients will improve after surgery. If, however, patients are ambulatory at the time of surgery, they may experience increased weakness after surgery. 

**Figure 606-9** T1-weighted MRI scan of a spinal cord tumor (arrow). The fusiform expansion of the cervical cord enhances after intravenous gadolinium injection.
They are likely to recover at least their preoperative level of function. Malignant spinal cord tumors are usually lethal with death resulting from diffuse metastases via the CSF pathways. Successful resection of nerve sheath tumors should be curative. In the context of neurofibromatosis, however, many more tumors can be found at other levels or can be expected to develop later in life. Surgical intervention in the context of neurofibromatoses should be performed only on clearly symptomatic lesions.

The outcome of treatment of extramedullary tumors depends on the cell type and, in most cases, on the efficacy of nonsurgical, adjunctive therapies. For aneurysmal bone cysts and giant cell tumors, resection of the tumor and fusion of the spine are the treatments of choice.

The significant majority of spinal cord tumors in children are benign (World Health Organization grades 2 and 3). The intramedullary low-grade gliomas for the most part act the same as the same histology in the brain. The evidence would point to the fact that intramedullary ependymomas act in a more benign fashion than they do in the fourth ventricle. Gross total removal without adjuvant treatment is the preferred method of treatment and carries not only much longer progression-free survival but improved quality of life as well.

Bibliography is available at Expert Consult.

606.5 Spinal Cord Injuries in Children
Harold L. Rekate

Spine and spinal cord injuries are very rare in children, particularly in young children. The spine of a small child is very mobile, and fractures of the spine are exceedingly rare. This increased mobility is not always a positive feature. Transfer of energy leading to spinal distortion can maintain the structural integrity of the spine but lead to significant injuries of the spinal cord. Spinal cord injury without radiographic bone (vertebral) abnormalities, called SCIWORA, is more common in children than adults. There seem to be 2 distinct forms. The infantile form involves severe injury of the cervical or thoracic spine. These patients have a poor likelihood of complete recovery. In older children and adolescents, SCIWORA is more likely to cause a less-severe injury and the likelihood of complete recovery over time is high. The adolescent form is assumed to be a spinal cord concussion or mild contusion as opposed to the severe spinal cord injury related to the mobility of the spine in small children.

Although the mechanisms of spinal cord injury in children include birth trauma, falls, and child abuse, the major cause of morbidity and mortality remains motor vehicle injuries. Although the mechanisms of injury and diagnosis are distinct in very small children, adolescents incur spinal cord injuries with epidemiology similar to that of adults, including significant male predominance and a high likelihood of fracture dislocations of the lower cervical spine or thoracoacromial region. In infants and children younger than age 5 yr, fractures and mechanical disruption of spinal elements are limited to the upper cervical spine between the occiput and C3.

CLINICAL MANIFESTATIONS
One in 3 patients with significant trauma to the spine and spinal cord will have a concomitant severe head injury, which makes early diagnosis challenging. For these patients clinical evaluation may be difficult. They need to be maintained in a protective environment such as a collar until the appropriate radiographs can be obtained. A careful neurologic examination is necessary for infants with suspected spinal cord injuries. Complete spinal cord injury will lead to spinal shock with early areflexia. Severe cervical spinal cord injuries will usually lead to paradoxical respiration in patients who are breathing spontaneously. Paradoxical respiration occurs when the diaphragm functions because the phrenic nerves from C3, C4, and C5 are functioning normally but the intercostal musculature innervated by the thoracic spinal cord is paralyzed. In this situation, inspiration fails to expand of the chest wall but distends the abdomen.

The mildest injury to the spinal cord is transient quadriparesis evident for seconds or minutes with complete recovery in 24 hr. This injury follows a concussion of the cord.

A transverse injury in the high cervical cord level (C1-C2) causes respiratory arrest and death in the absence of ventilatory support. Fracture dislocations at the C5-C6 level resulting in spinal cord injuries are characterized by flaccid quadriparesis, loss of sphincter function, and a sensory level corresponding to the upper sternum. Fractures or dislocations in the low thoracic (T12-L1) region may produce the conus medullaris syndrome, which includes a loss of urinary and rectal sphincter control, flaccid weakness, and sensory disturbances of the legs. A central cord lesion may result from contusion and hemorrhage and typically involves the upper extremities to a greater degree than the legs. There are lower motor neuron signs in the upper extremities and upper motor neuron signs in the legs, bladder dysfunction, and loss of sensation caudal to the lesion. There may be considerable recovery, particularly in the lower extremities.

Thoracolumbar injuries are usually fracture–dislocations such as occur in severe motor vehicle accidents when children are wearing lap belts but not shoulder harnesses. These injuries lead to a conus medullaris syndrome. These patients exhibit a loss of bowel and bladder function and lower motor neuron injuries involving the innervation of the lower extremities.

CLEARING THE CERVICAL SPINE IN CHILDREN
The management of children following major trauma is challenging. Clearing the cervical spine in children carries some of the same issues as it does in comatose adults in that with small children you cannot count on their cooperation with positioning for radiographs and complaints of pain are difficult to assess. There has been an increasing emphasis on the use of MRI for the evaluation of potential cervical spine instability but in small children this study requires sedation and, in most centers, the presence of an anesthesiologist. Despite the radiation dose, it is clear that the CT scan is the most important study with 100% sensitivity and 95% specificity. A multiply injured child is likely to be in the scanner having other anatomic studies done in any case and no other study has been shown to be better for detection of unstable cervical spine injury. This test detects all significant injuries to the cervical spine and has very few false-positives as opposed to MRI scanning, which overcalls the injury 1 in 4 times.

TREATMENT
The initial management of spine and spinal cord injuries in children is similar to that in adults. The cervical spine should be immobilized in the field by the emergency medical technicians. In cases of acute spinal cord injury, some data support the acute infusion of a bolus of high-dose (30 mg/kg) methylprednisolone followed by a 23 hr infusion (5.4 mg/kg/hr). The data for this treatment in children are controversial.

Surgical management of unstable spinal injuries must be tailored to the patient’s age. For occipitocervical dislocations, early surgery with fusion from the occiput to C2 or C3 should be performed, even in babies older than 6 mo. Fixation of the subaxial spine must be tailored to the size of the pedicles and other osseous structures of the developing axial skeleton.

PREVENTION
The most important aspect of the care of spinal cord injuries in children relates to injury prevention. In this regard, the use of appropriate child restraints in automobiles is the most important precaution. In older children and adolescents, rules against spear tackling in football and the “Feet First, First Time Program” from the Think First Foundation aimed at adolescents diving into swimming pools and natural water areas are important ways to help prevent severe cervical spinal cord injuries.

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

Bibliography


Transverse myelitis (TM) is a condition characterized by rapid development of both motor and sensory deficits at any level of the spinal cord. TM presents acutely as either partial or complete cord involvement and is defined as evidence of spinal cord inflammation by an MRI-documented enhancing lesion, or CSF pleocytosis (>10 cells), or increased immunoglobulin G index. The progression is rapid and the time to maximal disability is more than 4 hr and fewer than 21 days. It has multiple causes and tends to occur in 2 distinct contexts. Small children, 3 yr of age and younger, develop spinal cord dysfunction over hours to a few days. They have a history of an infectious disease, usually of viral origin, or of an immunization within the few weeks preceding the development of their neurologic difficulties. The clinical loss of function is often severe and may seem complete. Although a slow recovery (weeks to months) is common in these cases, it is likely to be incomplete. The likelihood of independent ambulation in these small children is approximately 40%. The pathologic findings of perivascular infiltration with mononuclear cells imply an infectious or inflammatory basis. Overt necrosis of spinal cord may rarely be seen. In older children, the syndrome is somewhat different. Although the onset is also rapid with a nadir in neurologic function occurring between 2 days and 2 wk, recovery is more rapid and more likely to be complete. Pathologic or imaging examination shows acute demyelination.

**CLINICAL MANIFESTATIONS**

TM is often preceded within the previous 1-3 wk by a mild nonspecific illness, minimal trauma, or perhaps an immunization. In both forms the patient shows or complains of discomfort or overt pain in the neck or back, depending on the level of the lesion. The most common involved segments are in the thoracic region. Depending on its severity, the condition progresses to numbness, anesthesia, ataxia, areflexia, and motor weakness in the truncal and appendicular musculature at or distal to the lesion. Paralysis begins as flaccidity (paraparesis, tetraparesis), but after a few weeks spasticity develops and is evident by hyperreflexia and clonus. Rarely is the weakness unilateral. Urinary retention is an early finding; incontinence occurs later in the course. Most have sensory loss manifest as anesthesia, paresthesia, or allodynia. Other findings may include priapism and vision loss (neuromyelitis optica), as well as spinal shock and subsequent autonomic dysreflexia.

The differential diagnosis includes demyelinating disorders, overt meningoitis, spinal cord infarction, or mass lesions such as bony distortion, abscess, and spine and spinal cord tumors (Table 606-1).

**DIAGNOSTIC EVALUATION**

MRI with and without contrast enhancement is essential to rule out a mass lesion requiring neurosurgical intervention. In both conditions, T1-weighted images of the spine at the anatomic level of involvement may be normal or may show distention of the spinal cord. In the infantile form, T2-weighted images show high signal intensity that extends over multiple segments. In the adolescent form, the high signal intensity may be limited to 1 or 2 segments. A limited degree of contrast enhancement after the administration of gadolinium is expected, especially in the infantile form, and denotes an inflammatory condition (Fig. 606-10). MRI of the brain is also indicated and shows evidence of other foci of demyelination in at least 30% of patients; in these patients and those with encephalopathy, acute disseminated encephalomyelitis must be considered (Fig. 606-11).

After a mass lesion associated with spinal cord compression or complete subarachnoid column block from spinal cord swelling have been ruled out, a lumbar puncture is indicated. In both forms of disease, the number of mononuclear cells is usually elevated. The level of CSF protein may be elevated or normal. CSF should be analyzed for myelin basic protein and immunoglobulin levels, which are usually elevated in TM. The presence of inflammatory cells is essential for the diagnosis of TM.

Because one of the most important possibilities for this condition is neuromyelitis optica (NMO; Devic syndrome) the serum of all patients should be analyzed for the NMO antibody. This test is positive in most patients with NMO (see Chapter 600.2). NMO is associated with bilateral optic neuritis and recurrent or long segment TM (≥3 segments). NMO may involve any spinal segment in addition to the brainstem or conus medullaris and cauda equina (myeloradiculitis). As in adults with

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**Table 606-1**

**Clinical and Radiologic Mimics of Transverse Myelitis**

<table>
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<tr>
<th>EXTRAXIAL COMPRESSION DISEASE</th>
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<td>a. Spinal cord tethering</td>
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<td>iii. Ewing sarcoma</td>
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<td>b. Abscess</td>
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<td>c. Carcinomatous infiltration</td>
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<td>4. Spinal nerve root inflammation</td>
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Figure 606-10 Transverse myelitis. A, Sagittal T2-weighted image demonstrates a longitudinal hyperintense spinal cord lesion spanning three vertebral segments (arrows). B, On an axial T2-weighted image, the lesion involves more than two-thirds of the cord’s cross-sectional area (arrow). C, Sagittal T1-weighted postcontrast image shows an enhancing area within the lesion (arrow). (From Ajtai B, Lindzen E, Masdeu JC: Structural imaging: magnetic resonance imaging and computed tomography. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors: Bradley’s neurology in clinical practice, ed 6. Philadelphia, 2012, WB Saunders, Fig. 33A.96.)

Figure 606-11 Acute disseminated encephalomyelitis. Sagittal T2-weighted image shows a diffuse hyperintense lesion spanning the length of the cervical cord (arrows). Note the enlarged caliber of the cord, which is a result of swelling. (From Ajtai B, Lindzen E, Masdeu JC: Structural imaging: magnetic resonance imaging and computed tomography. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors: Bradley’s neurology in clinical practice, ed 6. Philadelphia, 2012, WB Saunders, Fig. 33A.95.)

TM, older children with the condition should have serum studies sent for autoimmune disorders, especially systemic lupus erythematosus.

TREATMENT
There are no standards for the treatment of TM. Available evidence suggests that modulation of the immune response may be effective in decreasing the severity and duration of the condition. The use of high-dose steroids, particularly methylprednisolone, is the initial approach to treatment of childhood forms of TM. If there is a poor response to high-dose steroids, other therapeutic approaches include intravenous immunoglobulin, plasma exchanges, rituximab, and cyclophosphamide.

Follow-up of children with TM often reveals poor ambulation, continued bowel or bladder symptoms and dysesthesias.

Bibliography is available at Expert Consult.

606.7 Spinal Arteriovenous Malformations
Harold L. Rekate

Arteriovenous malformations of the spinal cord are rare lesions in children. Only about 60 patients younger than age 18 yr are treated in the United States each year. These lesions are complex. Despite their rarity there are multiple subtypes, which require different treatment strategies. Patients commonly present with back or neck pain, depending on the segments of the spinal cord involved, and they may experience the insidious onset of motor and sensory disturbances. Sudden onset of paraplegia secondary to hemorrhage has been reported. Occasionally, patients present with subarachnoid hemorrhage without overt neurologic deficits, similar to the presentation associated with cerebral aneurysms. In some cases, bruits are audible upon auscultation over the bony spine.

DIAGNOSTIC EVALUATION
When a spinal arteriovenous malformation is suspected, MRI of the spinal cord is first needed to make the diagnosis and to obtain a general idea of the location of the lesion. MR angiography or CT angiography may provide further information, but formal catheter angiography of the spinal cord is needed to obtain an adequate understanding of the complex anatomy of the lesion and to plan the intervention.

TREATMENT
Open microsurgery had been the mainstay of treatment for spinal cord arteriovenous fistulas and arteriovenous malformations. With the rapid development of interventional techniques, the percentage of patients undergoing microsurgery has decreased from 70% to approximately 30%. Stereotactic radiosurgery may be used adjunctively. Treatment of these complex lesions requires the commitment of an organized neurovascular treatment program.
Bibliography

The term **neuromuscular disease** defines disorders of the motor unit and excludes influences on muscular function from the brain, such as spasticity. The motor unit has 4 components: a motor neuron in the brainstem or ventral horn of the spinal cord; its axon, which together with other axons forms the peripheral nerve; the neuromuscular junction; and all muscle fibers innervated by a single motor neuron. The size of the motor unit varies among different muscles and with the precision of muscular function required. In large muscles, such as the glutei and quadriceps femoris, hundreds of muscle fibers are innervated by a single motor neuron; in small, finely tuned muscles, such as the stapedius or the extraocular muscles, a 1:1 ratio can prevail.

The motor unit is influenced by suprasegmental or upper motor neuron control that alters properties of muscle tone, precision of movement, reciprocal inhibition of antagonistic muscles during movement, and sequencing of muscle contractions to achieve smooth, coordinated movements. Suprasegmental impulses also augment or inhibit the monosynaptic stretch reflex; the corticospinal tract is inhibitory upon this reflex.

Diseases of the motor unit are common in children. These neuromuscular diseases may be genetically determined, congenital or acquired, acute or chronic, and progressive or static. Because specific therapy is available for many diseases and because of genetic and prognostic implications, precise diagnosis is important; laboratory confirmation is required for most diseases because of overlapping clinical manifestations.

Many chromosomal loci are identified with specific neuromuscular diseases as a result of genetic linkage studies and the isolation and cloning of a few specific genes. In some cases, such as Duchenne muscular dystrophy, the genetic defect is a deletion of nucleotide sequences and is associated with a defective protein product, dystrophin. In other cases, such as myotonic muscular dystrophy, the genetic defect is an expansion or repetition, rather than a deletion, in a codon (a set of 3 consecutive nucleotide repeats that encodes for a single amino acid), with many copies of a particular codon (in this example they are also associated with abnormal messenger RNA). Some diseases manifest as autosomal dominant and autosomal recessive traits in different pedigrees; these distinct mendelian genotypes can result from different genetic mutations on different chromosomes (nemaline myopathy) or from small differences in the same gene at the same chromosomal locus (myotonia congenita), despite many common phenotypic features and shared histopathologic findings in a muscle biopsy specimen. Among the several clinically defined mitochondrial myopathies, specific mitochondrial DNA deletions and transfer RNA point mutations are recognized. The inheritance patterns and chromosomal and mitochondrial loci of common neuromuscular diseases affecting infants and children are summarized in Table 608-1 in Chapter 608.

**CLINICAL MANIFESTATIONS**

Examination of the neuromuscular system includes an assessment of muscle bulk, tone, and strength. Tone and strength should not be confused: **Passive tone** is range of motion around a joint; **active tone** is physiologic resistance to movement. Head lag when an infant is pulled to a sitting position from supine is a sign of weakness, not of low tone. Hypotonia may be associated with normal strength or with weakness; enlarged muscles may be weak or strong; thin, wasted muscles may be weak or have unexpectedly normal strength. The distribution of these components is of diagnostic importance. In general, myopathies follow a proximal distribution of weakness and muscle wasting (with the notable exception of myotonic muscular dystrophy); neuropathies are generally distal in distribution (with the notable exception of juvenile spinal muscular atrophy; Table 607-1). Involvement of the face, tongue, palate, and extraocular muscles provides an important distinction in the differential diagnosis. **Tendon stretch reflexes** are generally lost in myopathies and in motor neuron diseases and are diminished but preserved in myopathies (Table 607-1). A few specific clinical features are important in the diagnosis of some neuromuscular diseases. **Fasciculations** of muscle, which are often best seen in the tongue, are a sign of denervation. Sensory abnormalities indicate neuropathy. Fatigable weakness is characteristic of neuromuscular junctional disorders. Myotonia is specific for a few myopathies.

Some features do not distinguish myopathy from neuropathy. **Muscle pain** or **myalgias** are associated with acute disease of either myopathic or neurogenic origin. Acute dermatomyositis and acute polyneuropathy (Guillain-Barré syndrome) are characterized by myalgias. Muscular dystrophies and spinal muscular atrophies are not associated with muscle pain. Myalgias also occur in several metabolic diseases of muscle and in ischemic myopathy, including vascular diseases such as dermatomyositis. Myalgias denote the acuity, rather than the nature, of the process, so that progressive but chronic diseases, such as muscular dystrophy and spinal muscular atrophy, are not painful but acute stages of inflammatory myopathies and acute denervation of muscle often do present with muscular pain and tenderness to palpation. **Contractures** of muscles, whether present at birth or developing later in the course of an illness, occur in both myopathic and neurogenic diseases.

Infant boys who are weak in late fetal life and in the neonatal period often have **undescended testes**. The testes are actively pulled into the scrotum from the anterior abdominal wall by a pair of cords that consist of smooth and striated muscle called the gubernaculum. The gubernaculum are weakened in many congenital neuromuscular diseases, including spinal muscular atrophy, myotonic muscular dystrophy, and many congenital myopathies.

The thorax of infants with congenital neuromuscular disease often has a funnel shape, and the ribs are thin and radiolucent as a result of intercostal muscle weakness during intrauterine growth. This phenomenon is characteristically found in infantile spinal muscular atrophy but also occurs in myotubular myopathy, neonatal myotonic dystrophy, and other disorders (Fig. 607-1). Because of the small muscle mass, birthweight may be low for gestational age.

Generalized hypotonia and motor developmental delay are the most common presenting manifestations of neuromuscular disease in infants and young children (Table 607-2). These features can also be expressions of neurologic disease, endocrine and systemic metabolic diseases, and Down syndrome, or they may be non-specific neuromuscular expressions of malnutrition or chronic systemic illness (Table 607-3). A prenatal history of decreased fetal movements and intrauterine growth retardation is often found in patients who are symptomatic at birth. Developmental disorders tend to be of slow onset and are progressive. Acute flaccid paralysis in older infants and children has a different differential diagnosis (Table 607-4).
LABORATORY FINDINGS

Serum Enzymes
Several lysosomal enzymes are released by damaged or degenerating muscle fibers and may be measured in serum. The most useful of these enzymes is creatine kinase (CK), which is found in only 3 organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is not a universal screening test for neuromuscular disease because many diseases of the motor unit are not associated with elevated enzymes. The CK level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy, and the magnitude of increase is characteristic for particular diseases.

<table>
<thead>
<tr>
<th>LOCUS OF LESION</th>
<th>WEAKNESS</th>
<th>PROXIMAL–DISTAL TENDON REFLEXES</th>
<th>ELECTROMYOGRAPHY</th>
<th>MUSCLE BIOPSY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>0</td>
<td>+</td>
<td>Normal or ↑</td>
<td>Normal</td>
<td>Seizures, hemiparesis, and delayed development</td>
</tr>
<tr>
<td>Ventral horn cell</td>
<td>Late</td>
<td>+++</td>
<td>0</td>
<td>Fasciculations and fibrillations</td>
<td>Denervation pattern</td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td>0</td>
<td>+++</td>
<td>↓</td>
<td>Fibrillations</td>
<td>Denervation pattern</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>+++</td>
<td>+++</td>
<td>Normal</td>
<td>Normal</td>
<td>Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism)</td>
</tr>
<tr>
<td>Muscle</td>
<td>Variable (+ to ++++)</td>
<td>++</td>
<td>↓</td>
<td>Short duration, small-amplitude motor unit potentials and myopathic polyphasic potentials</td>
<td>Myopathic pattern*</td>
</tr>
</tbody>
</table>

*Can also show unique features, such as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.  
+ to ++++, varying degrees of severity; BSAP, brief duration, small amplitude, overly abundant motor unit potentials.


Figure 607-1 Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Characteristic postures in 6 wk old (A) and 1 yr old (B) infants with severe weakness and hypotonia from birth. Note the frogleg posture of the lower limbs and internal rotation (“jug handle”) (A) or external rotation (B) at the shoulders. Note also intercostal recession, especially evident in B, and normal facial expressions. (From Volpe J: Neurology of the newborn, ed 4, Philadelphia, 2001, WB Saunders, p. 645.)
Molecular Genetic Markers
Many DNA markers of hereditary myopathies, including the muscular dystrophies, and neuropathies are available from leukocytes in blood samples. If the clinical manifestations suggest a particular disease, these tests can provide a definitive diagnosis and not subject the child to more-invasive procedures, such as muscle biopsy. Other molecular markers are available only in muscle biopsy tissue.

Nerve Conduction Velocity
Motor and sensory nerve conduction velocity may be measured electrophysiologically by using surface electrodes. Neuropathies of various types are detected by decreased conduction. The site of a traumatic nerve injury may also be localized. The nerve conduction value at birth is about half of the mature value achieved by age 2 yr. Tables are available for normal values at various ages in infancy, including for preterm infants. Because the nerve conduction velocity study measures only the fastest conducting fibers in a nerve, 80% of the total nerve fibers must be involved before slowing in conduction is detected.

Electromyography
Electromyography (EMG) requires insertion of a needle into the belly of a muscle and recording of the electric potentials in various states of contraction. It is less useful in pediatrics than in adult medicine, in part because of technical difficulties in recording these potentials in young children and in part because the best results require the patient's cooperation for full relaxation and maximal voluntary contraction of a muscle. Many children are too frightened to provide such cooperation. Characteristic EMG patterns distinguish denervation from myopathic involvement. The specific type of myopathy is not usually distinguishable, but certain specialized myopathic conditions, such as myotonia, may be demonstrated. An EMG can transiently raise the serum CK level.

EMG combined with repetitive electrical stimulation of a motor nerve supplying a muscle to produce tetany is useful in demonstrating myasthenic decremental responses. Small muscles, such as the abductor digiti quinti of the hypothenar eminence, are used for such studies. Additional specialized tests, such as single myofiber EMG, may provide supplementary evidence in selected cases, but are performed only in large neuromuscular centers.

Imaging of Muscle and Central Nervous System
Ultrasoundography, CT scans, and, more often, MRI are used to image muscle in many neuromuscular diseases. Although these methods are not always definitively diagnostic, in experienced hands, they provide a supplementary means of following the progression of disease over time. MRI is quite useful in identifying inflammatory myopathies of immune (dermatomyositis) or infectious (viral, bacterial, parasitic) origin. MRI is the study of choice to image the spinal cord, if a tumor or other structural lesion of the spinal cord is suspected as the cause of muscular dysfunction, and nerve roots and plexus (e.g., brachial plexus). Brain MRI is indicated in some myopathies, such as the congenital muscular dystrophies, in which cerebral malformations often accompany the myopathy because the mutated gene responsible is expressed in both muscle and the developing brain.

Muscle Biopsy
The muscle biopsy is traditionally the most important and specific diagnostic study of most neuromuscular disorders, if the definitive diagnosis of a hereditary disease is not provided by molecular genetic testing in blood. Not only are neurogenic and myopathic processes distinguished, but also the type of myopathy and specific enzymatic deficiencies may be determined. The vastus lateralis (quadriceps femoris) is the muscle that is most commonly sampled. The deltoid muscle should be avoided in most cases because it normally has a 60-80% predominance of type I fibers so that the distribution patterns of fiber types are difficult to recognize. Muscle biopsy is a simple outpatient procedure that may be performed under local anesthesia with or without femoral nerve block. Needle biopsies are preferred in some centers but are not percutaneous and require an incision in the skin similar to open biopsy; numerous samples must be taken to conduct an adequate examination of the tissue, and they provide inferior specimens. The volume of tissue from a needle biopsy is usually not adequate for all required studies, including supplementary biochemical studies, such as mitochondrial respiratory chain enzymes; a small, clean, open biopsy is therefore advantageous.

Histochemical studies of frozen sections of the muscle are obligatory in all pediatric muscle biopsies because many congenital and metabolic myopathies cannot be diagnosed from paraffin sections using conventional histologic stains. Immunohistochemistry is a useful supplement in some cases, such as for demonstrating dystrophin in suspected Duchenne muscular dystrophy or merosin in congenital muscular dystrophy. A portion of the biopsy specimen should be fixed for potential electron microscopy, but ultrastructure has additional diagnostic value only in selected cases. Interpretation of muscle biopsy samples is complex and should be performed by an experienced pathologist. A portion of frozen muscle tissue should also be routinely saved for possible biochemical analysis (mitochondrial cytopathies, carnitine palmitoyltransferase, acid maltase).

Immunocytochemical reactivities can be applied to formalin-fixed, paraffin-embedded sections and do not require frozen sections. Some reactivities, such as slow and fast myosin, can distinguish fiber types and hence substitute for myofibrillar adenosine triphosphatase histochemical stains in frozen sections. An increasing number of sarcolemmal regional proteins can be demonstrated that are specific for

### Table 607-2 Pattern of Weakness and Localization in the Floppy Infant

<table>
<thead>
<tr>
<th>ANATOMIC REGION OF HYPOTONIA</th>
<th>CORRESPONDING DISORDERS</th>
<th>PATTERN OF WEAKNESS AND INVOLVEMENT</th>
</tr>
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<tr>
<td>Central nervous system</td>
<td>Chromosomal disorders</td>
<td>Central hypotonia</td>
</tr>
<tr>
<td></td>
<td>Inborn errors of metabolism</td>
<td>Axial hypotonia more prominent</td>
</tr>
<tr>
<td></td>
<td>Cerebral dysgenesis</td>
<td>Hyperactive reflexes</td>
</tr>
<tr>
<td>Motor neuron</td>
<td>Spinal muscular atrophy</td>
<td>Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters</td>
</tr>
<tr>
<td>Nerve</td>
<td>Peripheral neuropathies</td>
<td>Distal muscle groups involved</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Myasthenia syndromes</td>
<td>Weakness with wasting</td>
</tr>
<tr>
<td></td>
<td>Infantile botulism</td>
<td>Bulbar, oculomotor muscles exhibit greater degree of involvement</td>
</tr>
<tr>
<td>Muscle</td>
<td>Congenital myopathies</td>
<td>Weakness is prominent</td>
</tr>
<tr>
<td></td>
<td>Metabolic myopathies</td>
<td>Proximal muscularity</td>
</tr>
<tr>
<td></td>
<td>Congenital muscular dystrophy</td>
<td>Hypoactive reflexes</td>
</tr>
<tr>
<td></td>
<td>Congenital myotonic dystrophy</td>
<td>Joint contractures</td>
</tr>
</tbody>
</table>

each of the various muscular dystrophies and include the dystrophins, merosin, sarcoglycans, and dystroglycans. Ryanodine receptors, important in myasthenia gravis and in malignant hyperthermia, also now can be demonstrated. In addition, immunocytochemical reactivities can distinguish the various types of inflammatory cells in autoimmune myopathies, including T and B lymphocytes and macrophages.

Nerve Biopsy
The most commonly sampled nerve is the sural nerve, a pure sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsy specimens of this nerve may be taken. When the sural nerve is severed behind the lateral malleolus of the ankle, regeneration of the nerve occurs in more than 90% of cases, so that permanent sensory loss is not experienced. The sural nerve is often involved in many neuropathies whose clinical manifestations are predominantly motor.

Electron microscopy is performed on most nerve biopsy specimens because many morphologic alterations cannot be appreciated at the resolution of a light microscope. Teased fiber preparations are sometimes useful in demonstrating segmental demyelination, axonal swellings, and other specific abnormalities, but these time-consuming procedures are not done routinely. Special stains may be applied to ordinary frozen or paraffin sections of nerve biopsy material to demonstrate myelin, axoplasm, and metabolic products.

The molecular genetic identification of the specific mutation in many of the hereditary motor and sensory neuropathies, determined from blood samples, has rendered the nerve biopsy much less often performed than in the past, but it retains a great value in selected cases for which the etiology remains elusive despite genetic and electrophysiological testing.

Cardiac Assessment
Cardiac evaluation is important if myopathy is suspected because of involvement of the heart in muscular dystrophies and in inflammatory and metabolic myopathies. Electrocardiography often detects early cardiomyopathy or conduction defects that are clinically asymptomatic. At times, a more complete cardiac work-up, including echocardiography and consultation with a pediatric cardiologist, is indicated. Serial pulmonary function tests also should be performed in muscular dystrophies and in other chronic or progressive diseases of the motor unit.

Bibliography is available at Expert Consult.
Bibliography


A heterogeneous group of congenital neuromuscular disorders is known as the **congenital myopathies** (Tables 608-1 and 608-2). Most of these disorders have subcellular abnormalities that can be demonstrated only by muscle biopsy, by means of histochemistry and electron microscopy. In others, the muscle biopsy abnormality is not a subcellular anatomic defect but an aberration in the ratio and sizes of specific myofiber types. A genetic basis is demonstrated in many of the congenital myopathies, and molecular genetic testing from blood samples may confirm the diagnosis without muscle biopsy.

Most congenital myopathies are nonprogressive conditions, but some patients show slow clinical deterioration accompanied by additional changes in their muscle histology. In some congenital myopathies, such as severe neonatal nemaline myopathy, the clinical expression can be life-threatening because of dysphagia and respiratory and/or cardiac insufficiency. Cardiomyopathy develops in some patients with congenital myopathies (Table 608-3). Most of the diseases in the category of congenital myopathies are hereditary; others are sporadic. Although clinical features, including phenotype, can raise a strong suspicion of a congenital myopathy, the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen. In conditions for which the defective gene has been identified, the diagnosis may be established by the specific molecular analysis of the suspected gene expressed in lymphocytes. The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies, spinal muscular atrophies, and neuropathies. Many are reminiscent of the embryologic development of muscle, thus suggesting possible defects in the genetic regulation of muscle development.

Congenital myopathies often show closer genetic relationships than previously appreciated between entities that have quite distinct pathologic phenotypes in the muscle biopsy and also distinctiveness in clinical expression with a degree of overlap. For example, mutation of the **tropomyosin-3** (**TPM3**) gene is one of the well-documented etiologies of nemaline myopathy, but identical genetic mutations of this gene are more recently also shown to be capable of causing isolated congenital fiber-type disproportion without nemaline rods, cap myopathy, centronuclear (“myotubular”) myopathy, and central core/minicore disease.

### MYOGENIC REGULATORY GENES AND GENETIC LOCI OF INHERITED DISEASES OF MUSCLE

A family of 4 myogenic regulatory genes shares encoding transcription factors of "basic helix-loop-helix" proteins associated with common DNA nucleotide sequences. These genes direct the differentiation of striated muscle from any undifferentiated mesodermal cell. The earliest basic helix-loop-helix gene to program the differentiation of myoblasts is **myogenic factor 5** (**MYF5**).

**Table 608-1** Classification of Muscular Dystrophies

<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>OMIM NUMBER</th>
<th>LOCUS</th>
<th>GENE SYMBOL</th>
<th>PROTEIN</th>
<th>MAIN LOCALIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne or Becker muscular dystrophy</td>
<td>X-R</td>
<td>310200 (Duchenne); 300376 (Becker)</td>
<td>Xq21-2</td>
<td>DMD</td>
<td>Dystrophin</td>
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<td>LIMB-GIRDLE MUSCULAR DYSTROPHY</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1A</td>
<td>AD</td>
<td>159000</td>
<td>5q31</td>
<td>MYOT</td>
<td>Myotilin</td>
</tr>
<tr>
<td>Type 1B</td>
<td>AD</td>
<td>159001</td>
<td>1q21-2</td>
<td>LMNA</td>
<td>Lamin A/C</td>
</tr>
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<td>Type 1C</td>
<td>AD</td>
<td>607780</td>
<td>3p25</td>
<td>CAV3</td>
<td>Caveolin-3</td>
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<td>Type 1D</td>
<td>AD</td>
<td>603511</td>
<td>7q</td>
<td>DNAJB6</td>
<td>Co-chaperone DNAJB6</td>
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<td>Type 1E</td>
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<td>602067</td>
<td>6q23</td>
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<td>Desmin</td>
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<td>7q32</td>
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<td>4p21</td>
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<td>Unknown</td>
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<td>Type 1H</td>
<td>AD</td>
<td>613530</td>
<td>3p23-p25</td>
<td>CAPN3</td>
<td>Calpain-3</td>
</tr>
<tr>
<td>Type 2A</td>
<td>AR</td>
<td>253600</td>
<td>15q15.1</td>
<td>DYSF</td>
<td>Dysferlin</td>
</tr>
<tr>
<td>Type 2B</td>
<td>AR</td>
<td>253601</td>
<td>2p13</td>
<td>SGCG</td>
<td>γ-Sarcoglycan</td>
</tr>
<tr>
<td>Type 2C</td>
<td>AR</td>
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<td>13q12</td>
<td>SGCx</td>
<td>α-Sarcoglycan</td>
</tr>
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<td>SGCA</td>
<td>β-Sarcoglycan</td>
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Text continued on p. 2970
### Table 608-1: Classification of Muscular Dystrophies—cont’d

<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>OMIM NUMBER</th>
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<th>GENE SYMBOL</th>
<th>PROTEIN</th>
<th>MAIN LOCALIZATION</th>
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<td>AR</td>
<td>601954</td>
<td>17q12</td>
<td>TCAP</td>
<td>Titin cap (telethonin)</td>
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<tr>
<td>Type 2H</td>
<td>AR</td>
<td>254110</td>
<td>9q31–q34</td>
<td>TRIM32</td>
<td>Tripartite motif-containing 32 (ubiquitin ligase) Fukutin-related protein</td>
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<tr>
<td>Type 2I</td>
<td>AR</td>
<td>607155</td>
<td>19q13-3</td>
<td>FKRP</td>
<td>Putative glycosyltransferase enzymes</td>
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<td>AR</td>
<td>608807</td>
<td>2q31</td>
<td>TTN</td>
<td>Protein-1-O-mannosyltransferase 1 Anoctamin 5</td>
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<td>Type 2K</td>
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<td>609308</td>
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<td>POMT1</td>
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<td>Type 2L</td>
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<td>611307</td>
<td>11p14-3</td>
<td>ANOS</td>
<td>Transmembrane protein, possible sarcoplasmic reticulum</td>
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<td>3p21</td>
<td>DAG1</td>
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**FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY**

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<tr>
<th>Type 1</th>
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<td>Type 2</td>
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**EMERY-DREIFUSS MUSCULAR DYSTROPHY**

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<th>X-linked type 1</th>
<th>X-R</th>
<th>310300</th>
<th>Xq28</th>
<th>EMD</th>
<th>Emerin</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked type 2</td>
<td>X-R</td>
<td>300696</td>
<td>Xq27-2</td>
<td>FHL1</td>
<td>Four and a half LIM domain 1 Lamin A/C</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>2181350</td>
<td>1q21-2</td>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>Nuclear membrane protein</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>604929</td>
<td>1q21-2</td>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>Nuclear membrane protein</td>
</tr>
<tr>
<td>With nesprin-1 defect</td>
<td>612998</td>
<td>6q25</td>
<td>SYNE1</td>
<td>Spectrin repeat containing, nuclear envelope 1 (nesprin-1)</td>
<td>Nuclear membrane protein</td>
</tr>
<tr>
<td>With nesprin-2 defect</td>
<td>5612999</td>
<td>4q23</td>
<td>SYNE2</td>
<td>Spectrin repeat containing, nuclear envelope 2 (nesprin-2)</td>
<td>Nuclear membrane protein</td>
</tr>
<tr>
<td>Congenital muscular dystrophy with merosin deficiency (MDC1A)</td>
<td>AR</td>
<td>607855</td>
<td>6q2</td>
<td>LAMA2</td>
<td>Laminin α2 chain of merosin</td>
</tr>
<tr>
<td>Congenital muscular dystrophy</td>
<td>AR</td>
<td>604801</td>
<td>1q42</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1C)</td>
<td>AR</td>
<td>606612</td>
<td>19q13</td>
<td>FKRP</td>
<td>Fukutin-related protein</td>
</tr>
<tr>
<td>Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1D)</td>
<td>AR</td>
<td>608840</td>
<td>22q12</td>
<td>LARGE</td>
<td>Like-glycosyl transferase</td>
</tr>
<tr>
<td>Fukuyama congenital muscular dystrophy</td>
<td>AR</td>
<td>253800</td>
<td>9q31–q33</td>
<td>FCMD</td>
<td>Fukutin</td>
</tr>
</tbody>
</table>

Continued
### Table 608-1 Classification of Muscular Dystrophies—cont’d

<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>OMIM NUMBER</th>
<th>LOCUS</th>
<th>GENE SYMBOL</th>
<th>PROTEIN</th>
<th>MAIN LOCALIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>WALKER–WARBURG SYNDROME</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With fukutin defect</td>
<td>AR</td>
<td>236670</td>
<td>9q31–q33</td>
<td>FCMD</td>
<td>Fukutin</td>
</tr>
<tr>
<td>With protein-O-mannosyltransferase 1 defect</td>
<td>AR</td>
<td>236670</td>
<td>9q34</td>
<td>POMT1</td>
<td>Protein-1-O-mannosyltransferase 1</td>
</tr>
<tr>
<td>With protein-O-mannosyltransferase 2 defect</td>
<td>AR</td>
<td>236670</td>
<td>14q24</td>
<td>POMT2</td>
<td>Protein-2-O-mannosyltransferase 2</td>
</tr>
<tr>
<td>With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect</td>
<td>AR</td>
<td>236670</td>
<td>1p34</td>
<td>POMGNT1</td>
<td>Protein-O-linked mannose β 1,2-N-aminyltransferase 1</td>
</tr>
<tr>
<td>With fukutin-related protein defect</td>
<td>AR</td>
<td>236670</td>
<td>19q13</td>
<td>FKRP</td>
<td>Fukutin-related protein</td>
</tr>
<tr>
<td>MUSCLE-EYE-BRAIN DISEASE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect</td>
<td>AR</td>
<td>253280</td>
<td>1p34</td>
<td>POMGNT1</td>
<td>Protein-1-O-linked mannose β 1,2-N-aminyltransferase 1</td>
</tr>
<tr>
<td>With fukutin-related protein defect</td>
<td>AR</td>
<td>253280</td>
<td>19q13</td>
<td>FKRP</td>
<td>Fukutin-related protein</td>
</tr>
<tr>
<td>With protein-O-mannosyltransferase 2 defect</td>
<td>AR</td>
<td>253280</td>
<td>14q24</td>
<td>POMT2</td>
<td>Protein-2-O-mannosyltransferase 2</td>
</tr>
<tr>
<td>Congenital muscular dystrophy caused by glycosylation disorder</td>
<td>AR</td>
<td>NA</td>
<td>9q34-1</td>
<td>DPM2</td>
<td>Dolichyl-phosphate mannosyltransferase polypeptide 2</td>
</tr>
<tr>
<td>Congenital muscular dystrophy caused by glycosylation disorder</td>
<td>AR</td>
<td>NA</td>
<td>1q21-3</td>
<td>DPM3</td>
<td>Dolichyl-phosphate mannosyltransferase polypeptide 3</td>
</tr>
<tr>
<td>Congenital muscular dystrophy with mitochondrial structural abnormalities</td>
<td>mtDNA</td>
<td>602541</td>
<td>22q13</td>
<td>CHKB</td>
<td>Choline kinase</td>
</tr>
<tr>
<td>Congenital muscular dystrophy with rigid spine syndrome</td>
<td>AR</td>
<td>602771</td>
<td>1p36</td>
<td>SEPN1</td>
<td>Selenoprotein N1</td>
</tr>
<tr>
<td>ULLRICH SYNDROME</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With collagen type VI subunit α1 defect</td>
<td>AR</td>
<td>254090</td>
<td>21q22.3</td>
<td>COL6A1</td>
<td>Collagen type VI, subunit α1</td>
</tr>
<tr>
<td>With collagen type VI subunit α2 defect</td>
<td>AR</td>
<td>254090</td>
<td>21q22.3</td>
<td>COL6A2</td>
<td>Collagen type VI, subunit α2</td>
</tr>
<tr>
<td>With collagen type VI subunit α3 defect</td>
<td>AR</td>
<td>254090</td>
<td>2q37</td>
<td>COL6A3</td>
<td>Collagen type VI, subunit α3</td>
</tr>
<tr>
<td>Congenital muscular dystrophy with integrin α7 defect</td>
<td>AR</td>
<td>613204</td>
<td>12q13</td>
<td>ITGA7</td>
<td>Integrin α7</td>
</tr>
<tr>
<td>Congenital muscular dystrophy with integrin α9 defect</td>
<td>AR</td>
<td>NA</td>
<td>3p21.3</td>
<td>ITGA9</td>
<td>Integrin α9</td>
</tr>
<tr>
<td>Muscular dystrophy with generalized lipodystrophy</td>
<td>AR</td>
<td>NA</td>
<td>17q21–q23</td>
<td>PTERF</td>
<td>Polyadenylate-binding protein nuclear 1</td>
</tr>
<tr>
<td>Oculopharyngeal muscular dystrophy</td>
<td>AD or AR</td>
<td>164300</td>
<td>14q11-2</td>
<td>PABPN1</td>
<td>Unknown</td>
</tr>
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</table>
# Table 608-2 Clinical Signs of Muscular Dystrophy

<table>
<thead>
<tr>
<th>MOTOR FUNCTION</th>
<th>DISTRIBUTION OF WEAKNESS</th>
<th>RIGID SPINE</th>
<th>CARDIOMYOPATHY</th>
<th>RESPIRATORY IMPAIRMENT</th>
<th>DISEASE COURSE</th>
<th>INCREASED CK</th>
<th>OTHER SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONGENITAL-ONSET MUSCULAR DYSTROPHY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital muscular dystrophy with merosin deficiency</td>
<td>Independent ambulation generally not achieved in patients with absent merosin</td>
<td>Upper limbs &gt; lower limbs</td>
<td>–</td>
<td>Not frequent</td>
<td>++</td>
<td>Slowly progressive</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White matter changes on brain MRI</td>
</tr>
<tr>
<td>Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (Walker-Warburg syndrome, muscle-eye-brain disease, congenital muscular dystrophy type 1C, etc.)</td>
<td>Independent ambulation generally not achieved</td>
<td>Upper limbs &gt; lower limbs</td>
<td>–</td>
<td>Not frequent</td>
<td>+</td>
<td>Slowly progressive</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequent structural brain changes</td>
</tr>
<tr>
<td>Congenital muscular dystrophy with rigid spine syndrome type 1 (SEPN1)</td>
<td>Ambulation achieved</td>
<td>Axial muscles &gt; limbs</td>
<td>++</td>
<td>–</td>
<td>Early respiratory failure</td>
<td>Progression of respiratory signs &gt; motor signs</td>
<td>N or +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Scoliosis</td>
</tr>
<tr>
<td>Ulrich syndrome</td>
<td>Ambulation achieved in ~50% but lost by middle teens</td>
<td>Proximal and axial</td>
<td>++</td>
<td>–</td>
<td>Early respiratory failure</td>
<td>Progression of respiratory and motor signs</td>
<td>N or +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Distal laxity</td>
</tr>
<tr>
<td><strong>FROM EARLY-ONSET TO CHILDHOOD-ONSET MUSCULAR DYSTROPHY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Independent ambulation achieved, but lost before age of 13 yr</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>Progression of motor, cardiac, and respiratory signs</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mental retardation in 30%</td>
</tr>
<tr>
<td>Emery-Dreifuss muscular dystrophy with lamin AC deficiency (type 2)</td>
<td>Ambulation achieved in all cases except for rare cases with congenital onset</td>
<td>Scapuloperoneal (pattern B)</td>
<td>++</td>
<td>++</td>
<td>In adulthood in the typical form, but also in childhood (congenital variants)</td>
<td>Slowly progressive</td>
<td>+ (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequent association with Dunningham-type lipodystrophy</td>
</tr>
<tr>
<td>Limb-girdle muscular dystrophy with lamin AC deficiency (type 1B)</td>
<td>Independent ambulation achieved, variable progression</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>+</td>
<td>++</td>
<td>In adulthood</td>
<td>Progression of cardiac signs &gt; motor signs</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Limb-girdle muscular dystrophy with calpain deficiency (type 2A)</td>
<td>Ambulation achieved</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>+</td>
<td>–</td>
<td>Not frequent</td>
<td>Slow progression</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Motor Function</th>
<th>Distribution of Weakness</th>
<th>Rigid Spine</th>
<th>Cardiomyopathy</th>
<th>Respiratory Impairment</th>
<th>Disease Course</th>
<th>Increased CK</th>
<th>Other Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Becker muscular dystrophy</strong></td>
<td>Independent ambulation achieved, variable progression</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>–</td>
<td>++</td>
<td>Not frequent</td>
<td>Progressive with substantial variability</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy</strong></td>
<td>Independent ambulation achieved, generally lost in the 2nd decade</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>Progression of motor, cardiac, and respiratory signs</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy with sarcoglycan deficiency</strong></td>
<td>Independent ambulation achieved, variable progression</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>–</td>
<td>++</td>
<td>(+)</td>
<td>Progressive</td>
<td>++</td>
<td>Mental retardation reported in some cases</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy with abnormal glycosylation of dystroglycan</strong></td>
<td>Independent ambulation achieved</td>
<td>Both pattern A and pattern E</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Progressive in adulthood</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy with dyserlin deficiency</strong></td>
<td>Independent ambulation achieved, generally lost in the 4th decade</td>
<td>Proximal &gt; distal (pattern A; in some pattern B)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Progressive in adulthood</td>
<td>+ (+)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy with t/tin deficiency</strong></td>
<td>Independent ambulation achieved</td>
<td>Proximal &gt; distal (pattern A but also pattern E)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Roughly half lose ambulation in adulthood</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td><strong>Facioscapulohumeral dystrophy</strong></td>
<td>Independent ambulation achieved, variable progression</td>
<td>Pattern D</td>
<td>–</td>
<td>–</td>
<td>Uncommon and mild</td>
<td>Slowly progressive</td>
<td>N or +</td>
<td>Neurosensory hearing loss and retinal degeneration</td>
</tr>
<tr>
<td><strong>Emery-Dreifuss muscular dystrophy with merin deficiency</strong></td>
<td>Independent ambulation achieved, variable progression</td>
<td>Scapuloperoneal (pattern B)</td>
<td>+</td>
<td>++</td>
<td>Not frequent</td>
<td>Progression of cardiac signs &gt; motor signs</td>
<td>+ (+)</td>
<td>None</td>
</tr>
<tr>
<td><strong>ADULT-ONSET MUSCULAR DYSTROPHY</strong></td>
<td></td>
<td>Mainly lower limbs pattern A, rarely pattern E</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Slowly progressive in adulthood</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy with anoctamin deficiency</strong></td>
<td>Onset in adulthood, 8:1 ratio of men to women</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Slowly progressive in adulthood</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy type 1A</strong> (myotilin)</td>
<td>Independent ambulation achieved</td>
<td>Proximal &gt; distal (pattern A)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Generally slowly progressive in adulthood</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy with caveolin deficiency</strong></td>
<td>Independent ambulation achieved; rippling might be seen before weakness</td>
<td>Proximal and distal</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>Slowly progressive, variable</td>
<td>++</td>
<td>Cramps, rippling, percussion-induced repetitive contractions</td>
</tr>
</tbody>
</table>

-- Absent; +, mild; ++, severe; (+), variable; CK, creatine kinase; N, normal.

*From Mercuri E, Muntoni F: Muscular dystrophies. Lancet 381:845-858, 2013, Table 2.*
### Table 608-3 Cardiac Involvement in Muscular Dystrophies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Onset and First Signs</th>
<th>Progression</th>
<th>Cardiac Death</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duchenne muscular dystrophy</strong></td>
<td>Dilated cardiomyopathy with reduced left-ventricular ejection fraction after 10 yr of age</td>
<td>Dilated cardiomyopathy in almost all patients by 18 yr of age. Ventricular dysrhythmias occur in older patients</td>
<td>Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established</td>
<td>Echocardiography every 2 yr in the 1st decade of life and annually after 10 yr of age (or more frequently if abnormalities are identified)</td>
</tr>
<tr>
<td><strong>Becker muscular dystrophy</strong></td>
<td>Dilated cardiomyopathy, generally after 10 yr of age</td>
<td>Present in 40% of patients older than 18 yr and more than 80% of those older than 40 yr. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias</td>
<td>Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported</td>
<td>Echocardiography at least every 5 yr</td>
</tr>
<tr>
<td><strong>Myotonic dystrophy</strong></td>
<td>Cardiac abnormalities can occur as early as the 2nd decade of life</td>
<td>Conduction deficits occur in about 65% of adult patients</td>
<td>20-30% of patients; mean 54 yr of age. Sudden death is mainly caused by conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death</td>
<td>ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias</td>
</tr>
<tr>
<td><strong>Emery-Dreifuss muscular dystrophy</strong></td>
<td>X-linked recessive Emery-Dreifuss muscular dystrophy (type 1)</td>
<td>Conduction disturbances generally in the 2nd decade</td>
<td>Sudden death is by far the most common cause of death and can be very unpredictable</td>
<td>ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops. Defibrillator might be needed in some patients</td>
</tr>
<tr>
<td><strong>Emery-Dreifuss muscular dystrophy 2 and limb-girdle muscular dystrophy 1B</strong></td>
<td>Conduction disease and cardiac failure</td>
<td>Ventricular myocardium might become involved, leading to mild ventricular dilation and low-to-normal systolic function</td>
<td>Sudden death reported also in patients with pacemaker. Rare death with defibrillator also reported. Cardiac failure. Cardiac transplants reported</td>
<td>ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered as pacemaker does not have a substantial effect on mortality</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy</strong></td>
<td>Sarcoglycanopathies</td>
<td>Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy-like dystrophy</td>
<td>Typically by cardiac failure. Cardiac transplants reported</td>
<td>No evidence-based standards of care exist, but experts have made recommendations</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy 2I</strong></td>
<td>Cardiac involvement reported in 29-62% of limb-girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage yr</td>
<td>Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)</td>
<td>Cardiac failure. Cardiac transplants reported</td>
<td>No evidence-based standards of care exist, but experts have made recommendations</td>
</tr>
<tr>
<td><strong>Limb-girdle muscular dystrophy 1E</strong></td>
<td>Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients</td>
<td>Typical cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness</td>
<td>Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 yr, including sudden death, end-stage heart failure, atrioventricular block, and syncope</td>
<td>No evidence-based standards of care exist, but experts have made recommendations</td>
</tr>
</tbody>
</table>

Continued
The fusion of myoblasts to form myotubes. Herculint (also known as MYF6) and MYOD1 are the other 2 myogenic genes. Myf5 cannot support myogenic differentiation without myogenin, MyoD, and MYF6. Each of these 4 genes can activate the expression of at least 1 other and, under certain circumstances, can autoregulate as well. Another recently discovered gene known as myomaker also facilitates myoblast fusion. The expression of MYF5 and of herculin is transient in early ontogenesis but returns later in fetal life and persists into adult life.

The human locus of the MYOD1 gene is on chromosome 11, very near to the domain associated with embryonal rhabdomyosarcoma. The genes Myf5 and herculin are on chromosome 12, and myogenin is on chromosome 1. The myogenic genes are activated during muscle regeneration, recapitulating the developmental process; MyoD in particular is required for myogenic stem cell (satellite cell) activation in adult muscle. PAX3, PAX7, and WNT3a genes also play important roles in myogenesis and interact with each of the 4 basic genes mentioned above. Another gene, myostatin, is a negative regulator of muscle development by preventing myocytes from differentiating. The precise integrative roles of the myogenic genes in developmental myopathies are not yet fully defined.

The myogenic genes are important not only for fetal myogenesis but also for regeneration of muscle at any age, particularly in degenerative diseases such as muscular dystrophies and autoimmune inflammatory myopathies and in injuries of muscle secondary to trauma or to toxins. Satellite cells in mature muscle that mediate regeneration have the same somatic origin as embryonic muscle progenitor cells, but the genes that regulate them differ. Pax3 and Pax7 mediate the migration of primitive myoblast progenitors from the myotomes of the somites to their peripheral muscle sites in the embryo, but only 1 of 2 Pax7 genes continues to act postnatally for satellite cell survival. Then it, too, no longer is required after the juvenile period for muscle satellite (i.e., stem) cells to become activated for muscle regeneration.

**Bibliography is available at Expert Consult.**

### 608.1 Myotubular Myopathy (Centronuclear Myopathy)

**Harvey B. Sarnat**

The term myotubular myopathy is a misnomer because it implies maturational arrest of fetal muscle during the myotubular stage of development at 8-15 wk of gestation. It was based on the morphologic appearance of myofibers as a row of central nuclei and mitochondria within a core of cytoplasm, with contractile myofilaments forming a cylinder around this core (Fig. 608-1). These morphologically abnormal myofibers are not true fetal myotubes, however; hence the more neutral and descriptive term centronuclear myopathy is preferred.

**PATHOGENESIS**

The common pathogenesis involves loss of myotubularin protein, leading to structural and functional abnormalities in the organization of T-tubules and sarcoplasmic reticulum and defective excitation-contraction coupling.

**CLINICAL MANIFESTATIONS**

Fetal movements can decrease in late gestation. Polyhydramnios is a common complication because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid.

At birth, affected infants have a thin muscle mass involving axial, limb girdle, and distal muscles; severe generalized hypotonia; and difficulty in swallowing amniotic fluid. Cervical spine flexion is low and the tongue is thin, but fasciculations are not seen. Tendon reflexes may be high. The tongue is thin, but fasciculations are not seen. Tendon stretch reflexes are weak or absent. Myotubular myopathy is not associated with cardiomyopathy (mature cardiac muscle fibers normally have central nuclei), but one report describes complete atrioventricular block without cardiomyopathy in a patient with confirmed X-linked myotubular myopathy. Congenital anomalies of the central nervous system or of other systems are not associated. A single patient with progressive dementia was reported, who had a mutation removing the start signal of exon 2. Patients with much milder symptoms or a much later age of onset with mutations in the same gene are now known. Some of these are manifesting carriers.

**LABORATORY FINDINGS**

Serum levels of creatine kinase (CK) are normal. Electromyography does not show evidence of denervation; results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. The
Bibliography


Developmental Disorders of Muscle

periphery of the muscle fiber in the term neonate as in the adult (hematoxylin and eosin, ×500). Myofibers have large central nuclei (B), and a term neonate with X-linked recessive myotubular myopathy (C). Myofibers have large central nuclei in the fetus and in myotubular myopathy patient, and nuclei are at the periphery of the muscle fiber in the term neonate as in the adult (hematoxylin and eosin, ×500).

electrocardiogram appears normal. Chest radiographs show no cardiomegaly; the ribs may be thin.

DIAGNOSIS
If the diagnosis is strongly suspected from the clinical presentation, especially if this diagnosis was confirmed in a sibling, genetic tests can be performed in the neonatal period. In most cases the diagnosis is not so evident, but the muscle biopsy findings are diagnostic at birth, even in premature infants. More than 90% of muscle fibers are small and have centrally placed, large vesicular nuclei in a single row. Spaces between nuclei are filled with sarcoplasm containing mitochondria. Histochemical stains for oxidative enzymatic activity and glycogen reveal a central distribution as in fetal myotubes. The cylinder of myofibrils shows mature histochemical differentiation with adenosine triphosphatase stains. The connective tissue of muscle spindles, blood vessels, intramuscular nerves, and motor end plates is mature. Ultrastructural features other than those that define the disease are also mature. Electron microscopy shows disorganized triads and focal loss of myofilaments. Vimentin and desmin show strong immunoreactivity in muscle fibers in congenital centronuclear myopathy and no demonstrable activity in normal term neonatal muscle. The molecular genetic marker in blood is available also for early prenatal diagnosis if suspicion is strong because of family history. Table 608-4 distinguishes centronuclear myopathy from other congenital myopathies.

GENETICS
At least 5 genes are involved in this disorder and account for approximately 80% of patients. These include mutations in myotubularin (MTM1 gene) with X-linked severe manifestations; dynamin 2 (DNM2) with autosomal dominant or sporadic occurrence; amphiphysin 2 (BIN1) and titin (TTN) mutations with autosomal recessive inheritance and ryanodine receptor 1 (RYR1), with autosomal recessive or sporadic occurrence.

X-linked recessive inheritance is the most common trait in this disease affecting boys. The mothers of affected infants are clinically asymptomatic, but their muscle biopsy specimens show minor alterations. Genetic linkage on the X chromosome has been localized to the Xq28 site, a locus different from the Xp21 gene of Duchenne and Becker muscular dystrophies. A deletion in the responsible MTM1 gene has been identified. It encodes a protein called myotubulin. This gene belongs to a family of similar genes encoding enzymatically active and inactive forms of phosphatidylinositol-3-phosphatases that form dimers. MTM1, dynamin-2, and amphiphysin all are localized to the T-tubule wall in triads. This crucial region is where the action potential releases a signal to the ryanodine receptor to release calcium. The pathogenesis is in the regulation of enzymatic activity and binding to other proteins induced by dimer interactions. Although only a single MTM1 gene is involved, 5 distinct point mutations and many different alleles, as well as large duplications, can produce the same clinical disease. Mutations in the dynamin-2 protein result in an autosomal dominant form of centronuclear myopathy and may account for up to half of all patients with centronuclear myopathy, but these cases usually are mild and might not manifest clinically until adult life as diffuse, slowly progressive weakness and generalized muscular pseudohypertrophy.

Other rarer centronuclear myopathies also are known; some are autosomal recessive and affect both sexes and others are sporadic and of unknown genetic origin. The recessive forms are sometimes divided into an early-onset form with or without ophthalmoplegia and a late-onset form without ophthalmoplegia.

TREATMENT
Only supportive and palliative treatment is presently available. Progressive scoliosis may be treated by long posterior fusion. Genetic and neuropathologic studies of X-linked centronuclear (“myotubular”) myopathy have led to effective gene therapy in mice and in dogs, so that even after a single dose the animals are more ambulatory and have much improved weakness. Gene replacement therapy in this disease is now being studied in humans.

PROGNOSIS
Approximately 75% of severely affected neonates with the X-linked disease die within the 1st few wk or mo of life. Survivors do not experience a progressive course but have major physical handicaps, rarely walk, and remain severely hypotonic. Late-onset and especially autosomal dominant forms have a much better prognosis, often with mild static weakness.

Bibliography is available at Expert Consult.


Congenital muscle fiber-type disproportion (CMFTD) occurs as an isolated congenital myopathy but also develops in association with various unrelated disorders that include nemaline rod disease, Krabbe disease (globoid cell leukodystrophy) early in the course before expression of the neuropathy, cerebellar hypoplasia and certain other brain malformations, fetal alcohol syndrome, some glycogenoses, multiple sulfatase deficiency, Lowe syndrome, rigid spine myopathy, and some infantile cases of myotonic muscular dystrophy. CMFTD should, therefore, be regarded as a syndrome, unless a specific genetic mutation is confirmed.

**PATHOGENESIS**

The association of CMFTD with cerebellar hypoplasia suggests that the pathogenesis may be an abnormal suprasegmental influence on the developing motor unit during the stage of histochemical differentiation of muscle between 20 and 28 wk of gestation. Muscle fiber types and growth are determined by innervation and are mutable even in adults. Although CMFTD does not actually correspond with any normal stage of development, it appears to be an embryologic disturbance of fiber type differentiation and growth.

**CLINICAL MANIFESTATIONS**

As an isolated condition not associated with other diseases, CMFTD is a nonprogressive disorder present at birth. Patients have generalized hypotonia and weakness, but the weakness is usually not severe and respiratory distress and dysphagia are rare. Contractures are present at birth in 25% of patients. Poor head control and developmental delay for gross motor skills are common in infancy. Walking is usually delayed until 18-24 mo but is eventually achieved. Because of the hypotonia, subluxation of the hips can occur. Muscle bulk is reduced. The muscle wasting and hypotonia are proportionately greater than the weakness, and the child may be stronger than expected during examination. Cardiomyopathy is a rare complication.

The facies of children with CMFTD often raise suspicion, especially if the child is referred for assessment of developmental delay and hypotonia. The head is dolichocephalic, and facial weakness is present. The palate is usually high arched. Thin muscles of the trunk and extremities give a thin, wasted appearance. The phenotype is very similar to that of nemaline myopathy that also includes CMFTD as part of the pathologic picture. Patients do not complain of myalgias. The clinical course is nonprogressive.

**LABORATORY FINDINGS**

Serum CK, electrocardiogram, electromyography, and nerve conduction velocity results are normal in simple CMFTD. If other diseases are associated, laboratory investigation of those conditions discloses the specific features.

**DIAGNOSIS**

CMFTD is diagnosed by muscle biopsy that shows disproportion in size and relative ratios of histochemical fiber types: Type I fibers are uniformly small, and type II fibers are hypertrophic; type I fibers are more numerous than type II fibers. Degeneration of myofibers and other primary myopathic features are absent. The biopsy is diagnostic at birth. Table 608-2 lists the features that distinguish CMFTD from other congenital myopathies.

**GENETICS**

Many cases of simple CMFTD are sporadic, although autosomal recessive inheritance is well documented in some families and an autosomal dominant trait is suspected in others. The genetic basis is heterogeneous in hereditary forms; a mutation in the insulin receptor gene at 19p13.2 is reported. Translocation t(10;17) was seen in 1 family. X-linked transmission with linkage to Xp23.12-p11.4 and Xq13.1-q22.1 also is described. In 3 unrelated families with CMFTD, a heterozygous missense mutation of the skeletal muscle α-actin gene (ACTA1) was demonstrated, but this genetic defect represents a minority; mutations in TPM3 are a more common genetic finding. As with X-linked myotubular myopathy, large duplications in the TPM3 gene can cause CMFTD. In CMFTD associated with cerebellar hypoplasia, the genetic effect is on cerebellar development and the muscular expression is secondary.

**TREATMENT**

No drug therapy is available. Physiotherapy may be helpful for some patients in strengthening muscles that do not receive sufficient exercise in daily activities. Mild congenital contractures often respond well to gentle range-of-motion exercises and rarely require plaster casting or surgery.

_Bibliography is available at Expert Consult._

**608.3 Nemaline Rod Myopathy**

_Neville B. Sarnat_

Nemaline rods (derived from the Greek _nema_, meaning “thread”) are rod-shaped, inclusion-like abnormal structures within muscle fibers. They are difficult to demonstrate histologically with conventional hematoxylin-and-eosin stain, but are easily seen with special stains. They are not foreign inclusion bodies but rather consist of excessive Z-band material with a similar ultrastructure (Fig. 608-2). Chemically, the rods are composed of actin, α-actinin, tropomyosin-3, and the protein nebulin. Nemaline rod formation may be an unusual reaction to injury because these rod structures have rarely been found in other diseases. They are most abundant in the congenital myopathy known as _nemaline rod disease_. Most rods are within the myofibrils, but intranuclear rods are occasionally demonstrated by electron microscopy. Intranuclear rods occur mainly in neonates with...
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The head is dolichocephalic, and the palate high arched or even cleft. Muscles of the jaw may be too weak to hold it closed (Fig. 608-4). Decreased fetal movements are reported by the mother, and neonates suffer from hypoxia and dysphagia; arthrogryposis may be present. Infants with severe neonatal and infantile nemaline myopathy have facies and phenotype that are nearly indistinguishable from those of neonatal myotonic dystrophy, but their mothers have normal facies. The juvenile form is the mildest and is not associated with respiratory failure, but the phenotype, including facial involvement, is similar.

LABORATORY FINDINGS
Serum CK level is normal or mildly elevated. The muscle biopsy is diagnostic. In addition to the characteristic nemaline rods, it also shows CMFTD or at least fiber type I predominance. In some patients, uniform type I fibers are seen with few or no type II fibers. Focal myofibrillar degeneration and an increase in lysosomal enzymes have been found in a few severe cases associated with progressive symptoms. Intranuclear nemaline rods, demonstrated by electron microscopy, correlate with the most severe neonatal manifestations. Because nemaline bodies can occur in other myopathies, their presence in the muscle biopsy is not pathognomonic in the absence of the supportive clinical manifestations. Adult-onset cases may be associated with monoclonal gammopathy.

GENETICS
Autosomal dominant and autosomal recessive forms of nemaline rod disease occur, and an X-linked dominant form in girls also can occur. Nemaline myopathy can be caused by mutation in at least 7 genes, including α-actin, α-tropomyosin, β-tropomyosin, troponin-T, nebulin, coflin-2, and Kelch-like family member (KLML40). The latter causes severe neonatal autosomal recessive nemaline myopathy. The proteins encoded for by all these genes are related to the thin filaments of myofibrils. Dominant nemaline myopathy is most often caused by mutations in ACTA-1 or α-tropomyosin (TPM3 at the 1q21-q23 locus); recessive mutations most frequently result from nebulin mutations (2q21.2-q22 locus), which account for about half the cases of nemaline myopathy and are particularly prevalent in Ashkenazi Jews. Some

CLINICAL MANIFESTATIONS
Neonatal, infantile, and juvenile forms of the disease are known. The neonatal form is severe and usually fatal because of respiratory failure since birth. In the infantile form, generalized hypotonia and weakness, which can include bulbar-innervated and respiratory muscles, and a very thin muscle mass are characteristic (Fig. 608-3).
mutations in the α-actin gene give rise to a severe neonatal myopathy with masses of exclusively thin filaments, with or without rods. Mutations in tropomyosin-2 can cause a congenital myopathy with nonspecific findings. In α-actin defects both autosomal dominant and recessive varieties occur at the same 1q42.1 locus. The autosomal dominantly inherited defect of β-tropomyosin at 9q13 and the α-tropomyosin defects are rare and account for only 3% of patients with nemaline myopathy. An autosomal recessive troponin-T defect is at locus 19q13 and has been found only in the Amish population, in whom the incidence of nemaline myopathy is as high as 1 in 500, whereas in Australia in non-Amish ethnic groups it is estimated at 1 in 500,000.

**TREATMENT AND PROGNOSIS**
Therapy is supportive. Survivors are confined to an electric wheelchair and are usually unable to overcome gravity. Both proximal and distal muscles are involved. Congenital arthrogryposis can occur and predicts a poor prognosis. Gastrostomy may be needed for chronic dysphagia. In the juvenile form, patients are ambulatory and are able to perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. Cardiomyopathy is an uncommon complication. Death usually results from respiratory insufficiency, with or without superimposed pneumonia.

*Bibliography is available at Expert Consult.*

### 608.4 Central Core, Minicore, and Multicore Myopathies

**Harvey B. Sarnat**

Central core disease most often manifests itself in children with slow motor development who are hypotonic and have mild weakness especially in the hip girdle; congenital dislocation or dysplasia of the hips may be diagnosed in the neonatal period. In older children, central core disease is an important differential diagnosis of progressive thoracolumbar scoliosis. Central core myopathies are transmitted as either an autosomal dominant or recessive trait and are caused by the same abnormal gene at the 19q13.1 locus. This gene programs the ryanodine receptor (RYR1), a tetrameric receptor that contains a non–voltage-gated calcium channel; it is prevalent in the sarcoplasmic reticulum and especially at the junction of the T-tubule with the cisternae of the sarcoplasmic reticulum. It contains the channel by which calcium is released among the myofilaments. Mutations in the RYR1 gene are also the cause of malignant hyperthermia.

Infantile hypotonia, proximal weakness, muscle wasting, and involvement of facial muscles and neck flexors are the typical features in both the dominant and recessive forms. Contractures of the knees, hips, and other joints are common, and kyphoscoliosis and pes cavus often develop, even without much axial or distal muscle weakness. There is a high incidence of cardiac abnormalities. The course is not progressive, except for the contractures. In one variant, external ophthalmoplegia also is present. Rare cases of minicore myopathy also show hypertrophic cardiomyopathy associated with short-chain acylcoenzyme A dehydrogenase deficiency.

The disease is characterized pathologically by central cores within muscle fibers in which only amorphous, granular cytoplasm is found with an absence of myofibrils and organelles. Histochemical stains show a lack of enzymatic activities of all types within these cores, as well as absence of contractile proteins (actin and myosin) that form the thin and thick myofilaments. Variants of central cores, called minicores and multicores, are described in some families.

Minicores or multicores are small areas, usually multiple within muscle fibers, that lack mitochondria and show Z-disc streaming. They can be caused by mutations in the gene (SEPN1) for the selenoprotein N, localized to triads, but RYR1 mutations also are reported. The distinction previously made between single and multiple cores is myofibers is now believed to be of little importance and they represent the same basic disease process.

The serum CK value is normal in central core disease except during crises of malignant hyperthermia, which can result in rhabdomyolysis or extensive acute myofiber necrosis (see Chapter 611.2). Central core disease is consistently associated with malignant hyperthermia, which can precede the diagnosis of central core disease. All patients should have special precautions with pretreatment with dantrolene before an anesthetic agent is administered.

*Bibliography is available at Expert Consult.*

### 608.5 Myofibrillar Myopathies

**Harvey B. Sarnat**

Most myofibrillar myopathies are not symptomatic in childhood, but occasionally older children and adolescents show early symptoms of nonspecific proximal and distal weakness. An infantile form also occurs and can cause mild neonatal hypotonia and weakness with disproportionately severe dysphagia and respiratory insufficiency, at times leading to early death. It is not progressive, however, and some patients show improvement in later infancy and early childhood, acquiring the ability to swallow by 3 yr of age. Cardiomyopathy is a complication in a minority.

The diagnosis is by muscle biopsy: some sarcomeres of myofibers have disorganization or dissolution of myofibrils adjacent to other areas of normal sarcomeres within the same fiber. These zones are associated with streaming of the Z bands and focally increased desmin intermediate filaments, myotitin, and αB-crystallin. Immunocytochemical and ultrastructural study of the muscle biopsy tissue is required. Mutation in the desmin gene is implicated as a contributory factor in the etiology of both adult-onset and childhood myofibrillar myopathies, but the primary defect is a mutation in, not just an upregulation of, the αB-crystallin molecule. An associated secondary mitochondrial defect is detected in some patients.

A unique autosomal recessive myopathy in Cree native infants is characterized by severe generalized muscular hypertonia that is not relieved by neuromuscular blockade and hence is myopathic in origin. Most die in infancy of respiratory insufficiency as a result of diaphragmatic involvement. The muscle biopsy shows findings similar to many other myofibrillar myopathies (Fig. 608-5); a novel αB-crystallin gene mutation is the cause.

*Bibliography is available at Expert Consult.*

![Figure 608-5 Electron micrograph of quadriceps femoris muscle biopsy of a 1 mo old native girl with Cree myofibrillar myopathy. Within the same myofiber, some sarcomeres are well formed and others exhibit disarray of the thick and thin myofilaments and fragmentation of Z bands. Mitochondria appear normal (×21,400).](image-url)
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608.6 Brain Malformations and Muscle Development
Harvey B. Sarnat

Infants with cerebellar hypoplasia are hypotonic and developmentally delayed, especially in gross motor skills. Muscle biopsy is sometimes performed to exclude a congenital myopathy. A biopsy specimen can show delayed maturation of muscle, fiber-type predominance, or CMFDTD. Other malformations of the brain may also be associated with abnormal histochemical patterns, but supratentorial lesions are less likely than brainstem or cerebellar lesions to alter muscle development. Abnormal descending impulses along bulbo spinal pathways probably alter discharge patterns of lower motor neurons that determine the histochemical differentiation of muscle at 20-28 wk of gestation. The corticospinal tract does not participate because it is not yet functional during this period of fetal life.

In several congenital muscular dystrophies (see Chapter 609.6), including the Walker-Warburg syndrome, Fukuyama disease, and muscle-eye-brain disease of Santavuori, major cerebral malformations, such as pachygyria and lissencephaly, are present. It is clear that in at least some of these cases, the abnormal protein implicated in pathogenesis of the syndrome is expressed in both muscle and brain and is important for both stabilization of muscle and migration of central neurons.

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608.7 Amyoplasia
Harvey B. Sarnat

Congenital absence of individual muscles is common and is often asymmetric. A common aplasia is the palmaris longus muscle of the ventral forearm, which is absent in 30% of normal subjects and is fully compensated for by other flexors of the wrist. Unilateral absence of a sternocleidomastoid muscle is one cause of congenital torticollis. Absence of 1 pectoralis major muscle is part of the Poland anomalad.

When innervation does not develop, as in the lower limbs in severe cases of myelomeningocele, muscles can fail to develop. In sacral agenesis, the abnormal somites that fail to form bony vertebrae can also fail to form muscles from the same defective mesodermal plate, a disorder of induction resulting in segmental amyoplasia. Skeletal muscles of the extremities fail to differentiate from embryonic myomeres if the long bones do not form. Absence of 1 long bone, such as the radius, is associated with variable aplasia or hypoplasia of associated muscles, such as the flexor carpi radialis. End-stage neurogenic atrophy of muscle is sometimes called amyoplasia, but this use is semantically incorrect.

Generalized amyoplasia usually results in fetal death, and liveborn neonates rarely survive. A mutation in 1 of the myogenic genes is the suspected etiology because of genetic knockout studies in mice, but it has not been proven in humans.

Bibliography is available at Expert Consult.

608.8 Muscular Dysgenesis (Proteus Syndrome Myopathy)
Harvey B. Sarnat

Proteus syndrome is a disturbance of cellular growth involving ectodermal and mesodermal tissues, representing a cellular mosaicism. The genetic defect is a mutation in the AKT1 gene, of the same genetic family as AKT3, which causes hemimegalencephaly; indeed many cases of Proteus syndrome also have hemimegalencephaly. These genes participate in the mammalian target of rapamycin pathway. Proteus syndrome also manifests as asymmetric overgrowth of the extremities, verrucous cutaneous lesions, angiomatas of various types, thickening of bones, and excessive growth of muscles without weakness. Severe seizures, beginning in neonates, are uncommon. Histologically, the muscle demonstrates a unique muscular dysgenesis. Abnormal zones are adjacent to zones of normal muscle formation and do not follow anatomic boundaries.

Bibliography is available at Expert Consult.

608.9 Benign Congenital Hypotonia
Harvey B. Sarnat

Benign congenital hypotonia is not a disease, but it is a descriptive term for infants or children with nonprogressive hypotonia of unknown origin. The hypotonia is not usually associated with weakness or developmental delay, although some children acquire gross motor skills more slowly than normal. Tendon stretch reflexes are normal or hypactive. There are no cranial nerve abnormalities, and intelligence is normal.

The diagnosis is one of exclusion (see Table 607-2 in Chapter 607) after results of laboratory studies, including muscle biopsy and imaging of the brain with special attention to the cerebellum, are normal. Muscle biopsy is deferred in some mild cases to follow the clinical evolution over time, but the diagnosis in these infants is more provisional. No known molecular genetic basis for this syndrome has been identified. Table 607-3 in Chapter 607 lists the differential diagnosis.

The prognosis is generally good; no specific therapy is required. Contractures do not develop. Physical therapy might help achieve motor milestones (walking) sooner than expected. Hypotonia persists into adult life. The disorder is not always as “benign” as its name implies because a common complication is recurrent dislocation of joints, especially the shoulders. Excessive motility of the spine can result in stretch injury, compression, or vascular compromise of nerve roots or of the spinal cord. These are particular hazards for patients who perform gymnastics or who become circus performers because of agility of joints without weakness or pain.

Bibliography is available at Expert Consult.

608.10 Arthrogryposis
Harvey B. Sarnat

Arthrogryposis multiplex congenita is not a disease but is a descriptive term that signifies multiple congenital contractures and is heterogeneous in etiology (see Chapter 682).

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Chapter 609
Muscular Dystrophies
Harvey B. Sarnat

The term dystrophy means abnormal growth, derived from the Greek trophe, meaning "nourishment." A muscular dystrophy is distinguished from all other neuromuscular diseases by 4 obligatory criteria: It is a primary myopathy, it has a genetic basis, the course is progressive, and degeneration and death of muscle fibers occur at some stage in the
Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, hypertrophy of the calves, and proliferation of connective tissue in muscle. The incidence is 1 in 3,600 liveborn infant boys. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. Becker muscular dystrophy (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

CLINICAL MANIFESTATIONS

Infant boys are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages or may be mildly delayed. Poor head control in infancy may be the first sign of weakness. Distinctive facies are not an early feature because facial muscle weakness is a late event; in later childhood, a "transverse" or horizontal smile may be seen. Walking is often accomplished at the normal age of approximately 12 mo, but hip girdle weakness may be seen in subtle form as early as the 2nd yr. Toddlers might assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers sign is often evident by age 3 yr and is fully expressed in brain and retina, as well as in striated and cardiac muscle, but there is no correlation with the severity of the myopathy. Epilepsy is slightly more common than in the general pediatric population. Autism-like behavior may develop but is uncommon. Duchenne muscular dystrophy is expressed in brain and retina, as well as in striated and cardiac muscle, though the level is lower in brain than in muscle. This distribution might explain some of the central nervous system manifestations. Abnormalities in cortical architecture and of dendritic arborization may be detected neuropathologically; cerebral atrophy is demonstrated by MRI late in the clinical course. The degenerative changes and fibrosis of muscle constitute a painless process. Myalgias and muscle spasms do not occur. Calcification of muscle is rare.

Death occurs usually at about 18-20 yr of age. The causes of death are respiratory failure during sleep, intractable heart failure, pneumonia, or, occasionally, aspiration and airway obstruction.

In BMD, boys remain ambulatory until late adolescence or early adult life. Cardiac assessment by echocardiography, electrocardiography (ECG), and radiography of the chest is essential and should be repeated.
periodically. After the diagnosis is established, patients should be referred to a pediatric cardiologist for long-term cardiac care.

Electromyography (EMG) shows characteristic myopathic features but is not specific for DMD. No evidence of denervation is found. Motor and sensory nerve conduction velocities are normal.

**DIAGNOSIS**

Polymerase chain reaction (PCR) for the dystrophin gene mutation is the primary test, if the clinical features and serum CK are consistent with the diagnosis. If the blood PCR is diagnostic, muscle biopsy may be deferred, but if it is normal and clinical suspicion is high, the more specific dystrophin immunocytochemistry performed on muscle biopsy sections detects the 30% of cases that do not show a PCR abnormality. Immunohistochemical staining of frozen sections of muscle biopsy tissue detects differences in the rod domain, the carboxyterminus (that attaches to the sarcolemma), and the aminoterminus (that attaches to the actin myofilaments) of the large dystrophin molecule, and may be prognostic of the clinical course as Duchenne or Becker disease. More-severe weakness occurs with truncation of the dystrophin molecule at the carboxy-terminus than at the aminoterminus. The diagnosis should be confirmed by blood PCR or muscle biopsy in every case. Dystroglycans and other sarcomemmal regional proteins, such as merosin and sarcoglycans, also can be measured because they may be secondarily decreased.

The **muscle biopsy** is diagnostic and shows characteristic changes (Figs. 609-1 and 609-2). Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still-functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level, allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary β-dystroglycan deficiency.

The decision about whether muscle biopsy should be performed to establish the diagnosis sometimes presents problems. If there is a family history of the disease, particularly in the case of an involved brother whose diagnosis has been confirmed, a patient with typical

**Figure 609-1** Muscle biopsy of a 4 yr old boy with Duchenne muscular dystrophy. Both atrophic and hypertrophic muscle fibers are seen, and some fibers are degenerating (deg). Connective tissue (c) between muscle fibers is increased (hematoxylin and eosin, ×400).

**Figure 609-2** Dystrophin is demonstrated by immunohistochemical reactivity in the muscle biopsies of a normal term male neonate (A), a 10 yr old boy with limb-girdle muscular dystrophy (B), a 6 yr old boy with Duchenne muscular dystrophy (C), and a 10 yr old boy with Becker muscular dystrophy (D). In the normal condition, and also in non–X-linked muscular dystrophies in which dystrophin is not affected, the sarcolemmal membrane of every fiber is strongly stained, including atrophic and hypertrophic fibers. In Duchenne dystrophy, most myofibers express no detectable dystrophin, but a few scattered fibers known as revertant fibers show near-normal immunoreactivity. In Becker muscular dystrophy, the abnormal dystrophin molecule is thin, with pale staining of the sarcolemma, in which reactivity varies not only between myofibers but also along the circumference of individual fibers (×250).
clinical features of DMD and high concentrations of serum CK probably does not need to undergo biopsy. The result of the PCR might also influence whether to perform a muscle biopsy. A first case in a family, even if the clinical features are typical, should have the diagnosis confirmed to ensure that another myopathy is not masquerading as DMD. The most common muscles sampled are the vastus lateralis (quadriceps femoris) and the gastrocnemius.

**GENETIC ETIOLOGY AND PATHOGENESIS**

Despite the X-linked recessive inheritance in DMD, approximately 30% of cases are new mutations, and the mother is not a carrier. The female carrier state usually shows no muscle weakness or any clinical expression of the disease, but affected girls are occasionally encountered, usually having much milder weakness than boys. These symptomatic girls are explained by the Lyon hypothesis in which the normal X chromosome becomes inactivated and the one with the gene deletion is active (see Chapter 80). The full clinical picture of DMD has occurred in several girls with Turner syndrome in whom the single X chromosome must have had the Xp21 gene deletion.

The asymptomatic carrier state of DMD is associated with elevated serum CK values in 80% of cases. The level of increase is usually in the magnitude of hundreds or a few thousand but does not have the extreme values noted in affected males. Prepubertal girls who are carriers of the dystrophy also have increased serum CK values, with highest levels at 8-12 yr of age. Approximately 20% of carriers have normal serum CK values. If the mother of an affected boy has normal CK levels, it is unlikely that her daughter can be identified as a carrier by measuring CK. Muscle biopsy of suspected female carriers can detect an additional 10% in whom serum CK is not elevated; a specific genetic diagnosis using PCR on peripheral blood is definitive. Some female carriers suffer cardiomyopathy without weakness of striated muscles.

A 427-kDa cytoskeletal protein known as dystrophin is encoded by the gene at the Xp21.2 locus. This gene contains 79 exons of coding sequence and 2.5 Mb of DNA, 10 times larger than the next largest gene yet identified. This subsarcolemmal protein attaches to the sarcolemmal membrane overlying the A and M bands of the myofibrils and consists of 4 distinct regions or domains: the amino terminus contains 250 amino acids and is related to the N-actin binding site of α-actinin; the second domain is the largest, with 2,800 amino acids, and contains many repeats, giving it a characteristic rod shape; a third, cysteine-rich domain is related to the carboxyl-terminus of α-actinin; and the final carboxyl-terminal domain of 400 amino acids is unique to dystrophin and to a dystrophin-related protein encoded by chromosome 6. “Dystrophin deficiency” at the sarcolemma disrupts the membrane cytoskeleton and leads to loss secondarily of other components of the cytoskeleton.

The molecular defects in the dystrophinopathies vary and include intragenic deletions, duplications, or point mutations of nucleotides. Approximately 65% of patients have deletions; approximately 10% exhibit duplications while approximately 10% have point mutations or smaller rearrangements. The site or size of the intragenic abnormality does not always correlate well with the phenotypic severity; in both Duchenne and Becker forms the mutations are mainly near the middle of the gene, involving deletions of exons 46-51. Phenotypic or clinical variations are explained by the alteration of the translational reading frame of messenger RNA (mRNA), which results in unstable, truncated dystrophin molecules and severe, classic DMD; mutations that preserve the reading frame still permit translation of coding sequences further downstream on the gene and produce a semifunctional dystrophin, expressed clinically as BMD. An even milder form of adult-onset disease, formerly known as quadriceps myopathy, is also caused by an abnormal dystrophin molecule. The clinical spectrum of the dystrophinopathies not only includes the classic Duchenne and Becker forms but also ranges from a severe neonatal muscular dystrophy to asymptomatic children with persistent elevation of serum CK levels >1,000 IU/L.

Analysis of the dystrophin protein requires a muscle biopsy and is demonstrated by Western blot analysis or in tissue sections by immunohistochemical methods using either fluorescence or light microscopy of antidystrophin antisera (see Fig. 609-2). In classic DMD, levels of <3% of normal are found; in BMD, the molecular weight of dystrophin is reduced to 20-90% of normal in 80% of patients, but in 15% of patients the dystrophin is of normal size but reduced in quantity, and 5% of patients have an abnormally large protein caused by excessive duplications or repeats of codons. Selective immunoreactivity of different parts of the dystrophin molecule in sections of muscle biopsy material distinguishes the Duchenne and Becker forms (Fig. 609-3). The demonstration of deletions and duplications also can be made from blood samples by the more rapid PCR, which identifies as many as 98% of deletions by amplifying 18 exons but cannot detect duplications. The diagnosis can thus be confirmed at the molecular genetic level from either the muscle biopsy material or from peripheral blood, although as many as 30% of boys with DMD or BMD have a false-normal blood PCR; all cases of dystrophinopathy are detected by muscle biopsy.

The same methods of DNA analysis from blood samples may be applied for carrier detection in female relatives at risk, such as sisters and cousins, and to determine whether the mother is a carrier or whether a new mutation occurred in the embryo. Prenatal diagnosis is possible as early as the 12th wk of gestation by sampling chorionic villi for DNA analysis by Southern blot or PCR and is confirmed in aborted fetuses with DMD by immunohistochemistry for dystrophin in muscle.

**TREATMENT**

There is no medical cure for this disease. Much can be done to treat complications and to improve the quality of life of affected children. Cardiac decompensation often responds initially well to digoxin. Pulmonary infections should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated.

Preservation of a good nutritional state is important. DMD is not a vitamin-deficiency disease, and excessive doses of vitamins should be avoided. Adequate calcium intake is important to minimize osteoporosis in boys confined to a wheelchair, and fluoride supplements may also be given, particularly if the local drinking water is not fluoridated. Because sedentary children burn fewer calories than active children and because depression is an additional factor, these children tend to eat excessively and gain weight. Obesity makes a patient with myopathy even less functional because part of the limited reserve muscle strength is dissipated in lifting the weight of excess subcutaneous adipose tissue. Dietary restrictions with supervision may be needed.

Physiotherapy delays but does not always prevent contractures. At times, contractures are actually useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90 degrees and the muscles of the upper limb no longer are strong enough to overcome gravity, the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily function, and exercise cannot further strengthen involved muscles. Excessive exercise can actually accelerate the process of muscle fiber degeneration.

Special vigilance should be maintained in watching for progressive scoliosis, which should be treated early by orthopedists using external braces or corsets and occasionally by surgeons. Scoliosis often becomes rapidly progressive once the patient is confined to a wheelchair.

Another recommended treatment of patients with DMD involves the use of prednisone, prednisolone, deflazacort, or other steroids. Glucocorticoids decrease the rate of apoptosis or programmed cell death of myotubes during ontogenesis and can decelerate the myofiber necrosis in muscular dystrophy. Strength usually improves initially, but the long-term complications of chronic steroid therapy, including
dystrophin protein. The shortened protein has been demonstrated to appear in muscle biopsies after treatment with these agents. Bibliography is available at Expert Consult.

609.2 Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy, also known as scapuloperoneal or scapulohumeral muscular dystrophy, is a rare X-linked recessive dystrophy. The usual locus of its associated genetic abnormality is on the long arm within the large Xq28 region that includes other mutations that cause myotubular myopathy, neonatal adrenoleukodystrophy, and the Bloch-Sulzberger type of incontinentia pigmenti; it is far from the gene for DMD on the short arm of the X chromosome. Another, rarer form of Emery-Dreifuss dystrophy is transmitted as an autosomal dominant trait and is localized at 1q. This form can manifest quite late, in adolescence or early adult life, although the muscular and cardiac symptoms and signs are similar, and sudden death from ventricular fibrillation is a risk.
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Bibliography
Clinical manifestations begin at between 5 and 15 yr of age, but many patients survive to late adult life because of the slow progression of the disease’s course. A rarer severe infantile presentation also is documented. Muscles do not exhibit pseudohypertrophy. Contractures of elbows and ankles develop early, and muscle becomes wasted in a scapulohumeroperoneal distribution. Facial weakness does not occur; this disease is thus distinguished clinically from autosomal dominant scapulohumeral and scapuloperoneal syndromes of neurogenic origin. Myotonia is absent. Intellectual function is normal. Dilated cardiomyopathy is severe and is often the cause of death, more commonly from conduction defects such as atrial fibrillation/flutter and sudden ventricular fibrillation than from intractable myocardial failure. Stroke is another complication, secondary to the cardiac arrhythmia. The serum CK value is only mildly to moderately elevated, further distinguishing this disease from other X-linked recessive muscular dystrophies.

Nonspecific myofiber necrosis and endomyocardial fibrosis are seen in the muscle biopsy. Many centronuclear fibers and selective histochemical type I muscle fiber atrophy can cause confusion with myotonic dystrophy.

GENETICS
The defective gene in the X-linked form is called EDMD or EDMD and encodes a protein, emerin. Unlike other dystrophies in which the defective gene is expressed at the sarcolemmal membrane, emerin is expressed at the inner nuclear membrane; this protein stabilizes the nuclear membrane against the mechanical stresses that occur during muscular contraction. It interacts with Nesprin-1 and Nesprin-2 genes, also critical for nuclear membrane integrity. Complete deletion of EDMD occurs in approximately 25% of cases and results from an inversion in the Xq28 region; total absence of emerin is demonstrated by both Western blotting and immunoreactivity in tissue sections. Another gene, LMNA, at the Xq21 locus, is linked to the nuclear envelop and encodes lamins A and C, sometimes termed laminopathy. This genetic mutation causes an identical clinical phenotype to EDMD defects, except that both sexes are affected and it is transmitted as either an autosomal dominant or recessive trait. Most EDMD deletions are null mutations, whereas most LMNA alterations are mainly missense mutations with a minority being nonsense or out-of-frame mutations. Desmin protein also may be mutated and seen to be abnormally expressed in the muscle biopsy. Homozygous nonsense mutations in these lamin A/C genes are lethal owing to cardiomyopathy and conduction disturbances.

DIAGNOSIS AND INVESTIGATIONS
In suspected cases, emerin deficiency may be demonstrated not only in the muscle biopsy by immunoreactivity and Western blotting techniques but also in a variety of other tissues, including circulating lymphocytes in peripheral blood, exfoliative buccal mucosal cells, and skin fibroblasts. Emerin is absent in varying proportions in female carriers. Genetic testing of the specific genes also is available. Patients should all have careful cardiac evaluation, including electrocardiogram and echocardiogram. Serum CK should be measured because it may be moderately elevated; though nonspecific, it provides a baseline for comparison with future measurements. Muscle MRI of the glutei and lower extremities may be helpful, particularly in LMNA mutations. EMG is not definitively diagnostic, but it provides a serial means of following the progression of the myopathy. Muscle biopsy is diagnostic from the onset of symptoms. In the differential diagnosis, an Emery-Dreifuss–like syndrome with joint contractures, mild weakness, and later-onset cardiac symptoms is caused by FHL1 mutations of myofibrillar myopathy, but reducing bodies are absent.

Treatment should be supportive, with special attention to cardiac conduction defects, and can require medications or a pacemaker. Implantable cardioverter-defibrillators are now available and have prevented sudden death in some patients with Emery-Dreifuss muscular dystrophy.

Bibliography is available at Expert Consult.

609.3 Myotonic Muscular Dystrophy
Harvey B. Sarnt

Myotonic dystrophy (Steinert disease) is the second most common muscular dystrophy in North America, Europe, and Australia, having an incidence varying from 1 in 100,000 to 1 in 300,000 in the general population. It is inherited as an autosomal dominant trait. Classic myotonic dystrophy (type 1) (DM1) is caused by a CTG trinucleotide expansion on chromosome 19q13.3 in the 3′ untranslated region of DMPK, the gene that encodes a serine-threonine protein kinase. Type 2 (DM2) is associated with unstable CCTG tetranucleotide repeat expansion on chromosome 3q21 of an intron of the zinc finger 9 protein gene. A third, late form (DM3) is identified, at locus 15q21-q24.

Myotonic dystrophy is an example of a genetic defect causing dysfunction in multiple organ systems. Not only is striated muscle severely affected, but smooth muscle of the alimentary tract and uterus is also involved, cardiac function is altered, and patients have multiple and variable endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, increased risk for malignancies, intellectual impairment, and other neurologic abnormalities.

CLINICAL MANIFESTATIONS
DM1 becomes symptomatic at any age, but DM2 is rarely expressed in infancy or early childhood. In the usual clinical course, excluding the severe neonatal form, DM1 infants can appear almost normal at birth, or facial wasting and hypotonia can already be early expressions of the disease. The facial appearance is characteristic, consisting of an inverted V-shaped upper lip, thin cheeks, and scalloped, concave temporalis muscles (Fig. 609-4). The head may be narrow, and the palate is high and arched because the weak temporal and pterygoid muscles in late fetal life do not exert sufficient lateral forces on the developing head and face.

Weakness is mild in the 1st few yr. Progressive wasting of distal muscles becomes increasingly evident, particularly involving intrinsic muscles of the hands. The thenar and hypothenar eminences are flattened, and the atrophic dorsal interossei leave deep grooves between the fingers. The dorsal forearm muscles and anterior compartment muscles of the lower legs also become wasted. The tongue is thin and atrophic. Wasting of the sternocleidomastoids gives the neck a long, thin, cylindrical contour. Proximal muscles also eventually undergo atrophy, and scapular winging appears. Difficulty with climbing stairs...
**Bibliography**


and Gowers sign are progressive. Tendon stretch reflexes are usually preserved.

The distal distribution of muscle wasting in myotonic dystrophy is an exception to the general rule of myopathies having proximal and neuropathies having distal distribution patterns. The muscular atrophy and weakness in myotonic dystrophy are slowly progressive throughout childhood and adolescence and continue into adulthood. It is rare for patients with myotonic dystrophy to lose the ability to walk even in late adult life, although splints or bracing may be required to stabilize the ankles.

Myotonia, a characteristic feature shared by few other myopathies, does not occur in infancy and is usually not clinically or even electromyographically evident until about age 5 yr. Exceptional patients develop it as early as age 3 yr. Myotonia is a very slow relaxation of muscle after contraction, regardless of whether that contraction was voluntary or was induced by a stretch reflex or electrical stimulation. During physical examination, myotonia may be demonstrated by asking the patient to make tight fists and then to quickly open the hands (grip myotonia; Fig. 609-5). It may be induced by striking the thenar eminence with a rubber percussion hammer (percuision myotonia), and it may be detected by watching the involuntary drawing of the thumb across the palm. Myotonia can also be demonstrated in the tongue by pressing the edge of a wooden tongue blade against its dorsal surface and by observing a deep furrow that disappears slowly. The severity of myotonia does not necessarily parallel the degree of weakness, and the weakest muscles often have only minimal myotonia. Myotonia is not a painful muscle spasm. Myalgias do not occur in myotonic dystrophy.

The speech of patients with myotonic dystrophy is often articulated poorly and is slurred because of the involvement of the muscles of the face, tongue, and pharynx. Difficulties with swallowing sometimes occur. Aspiration pneumonia is a risk in severely involved children. Incomplete external ophthalmoplegia sometimes results from extraocular muscle weakness.

Smooth muscle involvement of the gastrointestinal tract results in slow gastric emptying, poor peristalsis, and constipation. Some patients have encopresis associated with anal sphincter weakness. Women with myotonic dystrophy can have ineffective or abnormal uterine contractions during labor and delivery.

Cardiac involvement is usually manifested as heart block in the Purkinje conduction system and arrhythmias (sudden death) rather than as cardiomyopathy, unlike most other muscular dystrophies. Atrial or ventricular tachyrhythmias have also resulted in sudden death in adults and older children.

Endocrine abnormalities involve many glands and appear at any time during the course of the disease so that endocrine status must be reevaluated annually. Hypothyroidism is common; hyperthyroidism occurs rarely. Adrenocortical insufficiency can lead to an Addisonian crisis even in infancy. Diabetes mellitus is common in patients with myotonic dystrophy; some children have a disorder of insulin release rather than defective insulin production. Onset of puberty may be precocious or, more often, delayed. Testicular atrophy and testosterone deficiency are common in adults and are responsible for a high incidence of male infertility. Ovarian atrophy is rare. Frontal baldness is also characteristic in male patients and often begins in adolescence.

Immunologic deficiencies are common in myotonic dystrophy. The plasma immunoglobulin G level is often low.

Cataracts often occur in myotonic dystrophy. They may be congenital, or they can begin at any time during childhood or adult life. Early cataracts are detected only by slit-lamp examination; periodic examination by an ophthalmologist is recommended. Visual evoked potentials are often abnormal in children with myotonic dystrophy and are unrelated to cataracts. They are not usually accompanied by visual impairment.

About half of the patients with myotonic dystrophy are intellectually impaired, but severe intellectual impairment is unusual. The remainder are of average or occasionally above-average intelligence. Epilepsy is not common. Cognitive impairment might result from accumulations of mutant DMPK mRNA and aberrant alternative splicing in cerebral cortical neurons. A higher than expected incidence of autism occurs in children with DM1.

A severe congenital form of myotonic dystrophy appears in a minority of involved infants born to mothers with symptomatic myotonic dystrophy. All patients with this severe congenital disease to date have had the DM1 form. Clubfoot deformities alone or more extensive congenital contractures of many joints can involve all extremities (arthrogryposis multiplex congenita) and even include the cervical spine. Generalized hypotonia and weakness are present at birth. Facial wasting is prominent. Infants can require gavage feeding or ventilator support for respiratory muscle weakness or apnea. Those requiring ventilation for <30 days often survive, and those with prolonged ventilation have an infant mortality of 25%. Children ventilated for <30 days have better motor, language, and daily activity skills than those requiring prolonged ventilation. One or both leaves of the diaphragm may be nonfunctional. The abdomen becomes distended with gas in the stomach and intestine because of poor peristalsis from smooth muscle weakness. The distention further compromises respiration. Inability to empty the rectum can compound the problem.

LABORATORY FINDINGS

The classic myotonic electromyogram is not found in infants but can appear in toddlers or children in the early school years. The levels of serum CK and other serum enzymes from muscle may be normal or only mildly elevated in the hundreds (never the thousands). ECG should be performed annually in early childhood. Ultrasound imaging of the abdomen may be indicated in affected infants to determine diaphragmatic function. Radiographs of the chest and abdomen and contrast studies of gastrointestinal motility may be needed.

Endocrine assessment should be undertaken to determine thyroid and adrenal cortical function and to verify carbohydrate metabolism (glucose tolerance test). Immunoglobulins should be examined, and, if needed, more extensive immunologic studies should be performed.

DIAGNOSIS

The primary diagnostic test is a DNA analysis of blood to demonstrate the abnormal expansion of the CTG or CCTG repeat. Prenatal diagnosis also is feasible. The muscle biopsy specimen in older children shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers, but degenerating fibers are usually few and widely scattered, and there is little or no fibrosis of muscle. Intramuscular fibers of muscle spindles are also abnormal. In young children with the common form of the disease, the biopsy specimen can even appear normal or at least not show myofiber necroses, which is a striking contrast with DMD. In the severe neonatal form of myotonic dystrophy, the muscle biopsy reveals maturation arrest in various stages of development.

Figure 609-5 The patient was asked to squeeze with both of his hands for several seconds and then suddenly release his grasp, and several seconds passed before full relaxation was achieved, an exam finding known as grip myotonia. (From Hughes BN, Hogue JS, Hsieh DT: Grip and percussion myotonia in myotonic dystrophy type 1, J Pediatr 164:1234, 2014.)
development in some and congenital muscle fiber-type disproportion in others. It is likely that the sarcolemmal membrane of muscle fibers not only has abnormal properties of electrical polarization but is also incapable of responding to trophic influences of the motor neuron. Muscle biopsy is not usually required for diagnosis, which in typical cases can be based on the clinical manifestations, including family history. Neonatal myotonic dystrophy must be distinguished from amyoplasia, congenital muscular dystrophy with or without merosin expression, congenital myasthenia gravis, spinal muscular atrophy, and arthrogyrosis secondary to oligohydramnios.

GENETICS

The genetic defect in myotonic muscular dystrophy is on chromosome 19 at the 19q13 locus. It consists of an expansion of the DM gene that encodes a serine-threonine kinase (DMPK), with numerous repeats of the CTG codon. Expansions range from 50 to >2,000, with the normal alleles of this gene ranging in size from 5-37; the larger the expansion, the more severe the clinical expression, with the largest expansions seen in the severe neonatal form. Rarely, the disease is associated with no detectable repeats, perhaps a spontaneous correction of a previous expansion but a phenomenon still incompletely understood. Another myotonic dystrophy (proximal myotonic myopathy) is a clinical entity linked to at least 2 different chromosomal loci than classic myotonic dystrophy but to 1 locus that shares a common unique pathogenesis in being mediated by a mutant mRNA. Defects in RNA splicing explain the insulin resistance in myotonic dystrophies as well as the myotonia.

Clinical and genetic expression can vary between siblings or between an affected parent and child. In the severe neonatal form of the disease, the mother is the transmitting parent in 94% of cases, a fact not explained by increased male infertility alone. Several cases of paternal transmission have been reported. Genetic analysis reveals that symptomatic neonates usually have many more repeats of the CTG codon than do patients with the more classic form of the disease, regardless of which parent is affected. Myotonic dystrophy often exhibits a pattern of anticipation in which each successive generation has a tendency to be more severely involved than the previous generation. Prenatal genetic diagnosis of myotonic dystrophy is available.

Treatment

There is no specific medical treatment, but the cardiac, endocrine, gastrointestinal, and ocular complications can often be treated. Physiotherapy and orthopedic treatment of contractures in the neonatal form of the disease may be beneficial. Myotonia may improve with exercise (warm-up phenomenon). Cardiac pacemaker implantation might be considered for heart block and antiarrhythmic drugs might be indicated but are needed only rarely in children.

Myotonia may be diminished, and function may be restored by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate. These drugs also have cardiotropic effects; thus, cardiac evaluation is important before prescribing them. Phenytoin and carbamazepine are used in doses similar to their use as antiepileptics (see Chapter 593.6); serum concentrations of 10-20 µg/mL for phenytoin and 5-12 µg/mL for carbamazepine should be maintained. If a patient's disability is caused mainly by weakness rather than by myotonia, these drugs will be of no value.

OTHER MYOTONIC SYNDROMES

Most patients with myotonia have myotonic dystrophy. However, myotonia is not specific for this disease and occurs in several rarer conditions.

Myotonic chondrodystrophy (Schwartz-Jampel disease) is a rare congenital disease characterized by generalized muscle hypertrophy and weakness. Dysmorphic phenotypical features and the radiographic appearance of long bones are reminiscent of Morquio disease (see Chapter 88), but abnormal mucopolysaccharides are not found. Dwarfism, joint abnormalities, and blepharophimosis are present. Several patients have been the products of consanguinity, suggesting autosomal recessive inheritance. The muscle protein perlecan, encoded by the SJS1 gene, a large heparan sulfate proteoglycan of basement membranes and cartilage, is defective in some cases of Schwartz-Jampel disease and explains both the muscular hyperexcitability and the chondrodysplasia. EMG reveals continuous electrical activity in muscle fibers closely resembling or identical to myotonia. Muscle biopsy reveals nonspecific

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<tr>
<th>Table 609-1</th>
<th>Channelopathies and Related Disorders</th>
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<td>PATTERN OF CLINICAL FEATURES</td>
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<tr>
<td>Malignant hyperthermia</td>
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myopathic features, which are minimal in some cases and pronounced in others. The sarcotubular system is dismantled.

Myotonia congenita (Thomsen disease) is a channelopathy (Table 609-1) and is characterized by weakness and generalized muscular hypertrophy so that affected children resemble bodybuilders. Myotonia is prominent and can develop at age 2-3 yr, earlier than in myotonic dystrophy. The disease is clinically stable and is apparently not progressive for many years. Muscle biopsy specimens show minimal pathologic changes, and the EMG demonstrates myotonia. Various families are described as showing either autosomal dominant (Thomsen disease) or recessive (Becker disease, not to be confused with BMD or DMD) inheritance. Rarely, myotonic dystrophy and myotonia congenita coexist in the same family. The autosomal dominant and autosomal recessive forms of myotonia congenita have been mapped to the same 7q35 locus. This gene is important for the integrity of chloride channels of the sarcolemmal and T-tubular membranes.

Paramyotonia is a temperature-related myotonia that is aggravated by cold and alleviated by warm external temperatures. Patients have difficulty when swimming in cold water or if they are dressed inadequately in cold weather. Paramyotonia congenita (Eulenburg disease) is a defect in a gene at the 17q13.1-13.3 locus, the identical locus identified in hyperkalemic periodic paralysis. By contrast with myotonia congenita, paramyotonia is a disorder of the voltage-gated sodium channel caused by a mutation in the α subunit. Myotonic dystrophy also is a sodium channelopathy (see Table 609-1).

In sodium channelopathies, exercise produces increasing myotonia, whereas in chloride channelopathies, exercise reduces the myotonia. This is easily tested during examination by asking patients to close the eyes forcefully and open them repeatedly; it becomes progressively more difficult in sodium channel disorders and progressively easier in chloride channel disorders.

Bibliography is available at Expert Consult.

609.4 Limb-Girdle Muscular Dystrophies

Harvey B. Sarnat

Limb-girdle muscular dystrophies (LGMDs) encompass a heterogeneous group of progressive hereditary muscular dystrophies that mainly affect muscles of the hip and shoulder girdles (Table 609-2). Distal muscles also eventually become atrophic and weak. Hypertrophy of the calves and ankle contractures develop in some forms, causing potential confusion with BMD. Sixteen genetic forms of LGMD are now described, each at a different chromosomal locus and expressing different protein defects. Some include diseases classified with other traditional groups, such as the lamin-A/C defects of autosomal recessive LGMD. Most sarcoglycanopathies result from a mutation in α-sarcoglycan; other LGMDs resulting from deficiencies in β-, γ-, and δ-sarcoglycan also occur. In normal smooth muscle, α-sarcoglycan is replaced by ε-sarcoglycan, and the others are the same. A dystroglycan mutation also is implicated in some cases. Another group of LGMDs (type 2B) are caused by allelic mutations of the dystrophin (DYSF) gene, another gene expressing a protein essential to structural integrity of the sarcolemma, though not associated with the dystrophin-glycoprotein complex. DYSF interacts with caveolin-3 or calpain-3, and DYSF deficiency may be secondary to defects in these other gene products. Primary calpain-3 defect (type 2A) is reported in Amish families and in families from French Reunion Island and from Brazil. Autosomal recessive (Miyoshi myopathy) and autosomal dominant traits are documented. Both are slowly progressive myopathies with onset in adolescence or young adult life and can affect distal as well as proximal muscles. Cardiomyopathy is rare. Chronically elevated serum CK in the thousands is found in dysferlinopathies. Ultrastructure shows a thickened basal lamina over defects in the sarcolemma and replacement of the sarcolemma by multiple

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<th>Table 609-2</th>
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<tr>
<td><strong>TYPE</strong></td>
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Bibliography
layers of small vesicles. Regenerating myofibers outnumber degenerat
myofibers. These disorders were formerly called hyperCKemia and rippling muscle disease, the latter sometimes confused with myotonia. An autosomal recessive mutation in the calcium-activated chloride channel anoctamin-5 can cause proximal LGMD2.

There is overlap of the group of LGMDs with the congenital muscular dystrophies, such as Walker-Warburg syndrome with POMT, Fukuyama muscular dystrophy with FKRP genetic defects, and Ullrich muscular dystrophy of collagen V1 subunits.

Bibliography is available at Expert Consult.

609.5 Facioscapulohumeral Muscular Dystrophy

Harvey B. Sarnat

Facioscapulohumeral muscular dystrophy, also known as Landouzy-Dejerine disease, is probably not a single disease entity but a group of diseases with similar clinical manifestations. Autosomal dominant inheritance is the rule; genetic anticipation is often found within several generations of a family, the succeeding more severely involved at an earlier age than the preceding. The frequency is 1:20,000 population. Though the clinical onset is generally in later childhood or adult life, early molecular defects arising during myogenesis are demonstrated in the human fetus. The genetic mechanism in autosomal dominant facioscapulohumeral dystrophy involves integral deletions of a 3.3-kb tandem repeat (D4Z4) in the subtelomeric region at the 4q35 locus. Several other genes clustered at the 4q35 locus are upregulated in fetuses with facioscapulohumeral dystrophy. D4Z4 acts as a lamin-dependent insulator exhibiting both enhancer-blocking and barrier activities and displaces the telomere toward the nuclear periphery. A 3.3-kb repeat array at the subtelomeric locus 10q26 is closely homologous, with chromosomal translocation or sequence conversion between these 2 regions, possibly predisposing to the DNA rearrangement causing facioscapulohumeral dystrophy. Approximately 10% of families with this phenotype do not map to the 4q35 locus.

CLINICAL MANIFESTATIONS

Facioscapulohumeral dystrophy shows the earliest and most severe weakness in facial and shoulder girdle muscles. The facial weakness differs from that of myotonic dystrophy; rather than an inverted V-shaped upper lip, the mouth in facioscapulohumeral dystrophy is rounded and appears puckered because the lips protrude. Inability to close the eyes completely in sleep is a common expression of upper facial weakness; some patients have extraocular muscle weakness, although ophthalmoplegia is rarely complete. Facioscapulohumeral dystrophy has been associated with Möbius syndrome on rare occasions. Pharyngeal and tongue weakness may be absent and is not as severe as the facial involvement. Hearing loss, which may be subclinical, and retinal vasculopathy (indistinguishable from Coats disease) are associated features, particularly in severe cases of facioscapulohumeral dystrophy with early-childhood onset.

Scapular winging is prominent, often even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdle and thighs also eventually lose strength and undergo atrophy, and Gowers sign and a Trendelenburg gait appear. Contractures of the extremities are rare. Finger and wrist weakness occasionally is the first symptom. Weakness of the anterior tibial and peroneal muscles can lead to footdrop; this complication usually occurs only in advanced cases with severe weakness. Lumbar lordosis and kyphoscoliosis are common complications of axial muscle involvement. Calf pseudohypertrophy is not a usual feature but is described rarely.

Facioscapulohumeral muscular dystrophy can also be a mild disease causing minimal disability. Clinical manifestations might not be expressed in childhood and are delayed into middle adult life. Unlike most other muscular dystrophies, asymmetry of weakness is common.

About 30% of affected patients are asymptomatic or show only mild scapular winging and decreased tendon stretch reflexes, of which they were unaware until formal neurologic examination was performed.

LABORATORY FINDINGS

Serum levels of CK and other enzymes vary greatly, ranging from normal or near-normal to elevations of several thousand. An ECG should be performed, although the anticipated findings are usually normal. EMG reveals nonspecific myopathic muscle potentials. Diagnostic molecular testing in individual cases and within families is indicated for prediction.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Molecular genetic diagnosis is the most specific confirmation if clinical suspicion is high, with or without a family history of the disease. Muscle biopsy distinguishes more than one form of facioscapulohumeral dystrophy, consistent with clinical evidence that several distinct diseases are embraced by the term facioscapulohumeral dystrophy. Muscle biopsy and EMG also distinguish the primary myopathy from a neurogenic disease with a similar distribution of muscular involvement. The general histopathologic findings in the muscle biopsy material are extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers. An "inflammatory" type of facioscapulohumeral muscular dystrophy is also distinguished, characterized by extensive lymphocytic infiltrates within muscle fascicles. Despite the resemblance of this form to inflammatory myopathies, such as polymyositis, there is no evidence of autoimmune disease, and steroids and immunosuppressive drugs do not alter the clinical course. A precise histopathologic diagnosis has important therapeutic implications. Mononuclear cell "inflammation" in a muscle biopsy sample of infants younger than 2 yr old is usually facioscapulohumeral dystrophy or, less often, a congenital muscular dystrophy.

TREATMENT

Physiotherapy is of no value in regaining strength or in retarding progressive weakness or muscle wasting. Footdrop and scoliosis may be treated by orthopedic measures. In selected cases, surgical wiring of the scapulas to the thoracic wall provides improved shoulder stability and abduction of the arm, but brachialplexopathy, frozen shoulder, and scapular fractures are reported complications. Cosmetic improvement of the facial muscles of expression may be achieved by reconstructive surgery, which grafts a fascia lata to the zygomatic muscle and to the zygomatic head of the quadratus labii superioris muscle. Exercise of facial muscles can help minimize secondary disuse atrophy. No effective pharmacologic or genetic treatment is presently available.

Bibliography is available at Expert Consult.

609.6 Congenital Muscular Dystrophies

Harvey B. Sarnat

The term congenital muscular dystrophy is misleading because all muscular dystrophies are genetically determined. It is used to encompass several distinct diseases that have a common characteristic of severe involvement at birth but that, ironically, often follow a more benign clinical course than the early onset and the histopathological changes in the muscle biopsy would suggest. A distinguishing feature of the congenital dystrophies, by contrast with other muscular dystrophies, is a high association with brain malformations, particularly disorders of cortical development such as lissencephaly/pachygyria and polymicrogyria, often complicated by severe epilepsy. Autosomal recessive inheritance is the rule.

CLINICAL MANIFESTATIONS

In several distinct clinical and genetic diseases grouped under the umbrella term congenital muscular dystrophies, infants often have
Bibliography


**Bibliography**


congenital muscular dystrophy and arthrogryposis at birth and are diffusely hypotonic. The muscle mass is thin in the trunk and extremities. Head control is poor. Facial muscles may be mildly involved, but ophthalmoplegia, pharyngeal weakness, and weak sucking are not common. A minority has severe dysphagia and requires gavage or gastrostomy. Tendon stretch reflexes may be hyporeactive or absent. Arthrogryposis is common in all forms of congenital muscular dystrophy (see Chapter 608.10). Congenital contractures of the elbows have a high association with the Ullrich type of congenital muscular dystrophy owing to a defect in 1 or more of the 3 collagen VI genes, each at a different locus.

The congenital muscular dystrophies can be classified according to the type of protein altered by the specific genetic mutations. Diseases of extracellular matrix proteins include merosin deficiency (LAMA2 mutation at locus 6q22-q23) and Ullrich disease (COL6A1, -A2 and -A3 mutations at 21q22 and 2q37 loci). A protein of the endoplasmic reticulum (SEPN1 mutation at 1p35) is the basis of rigid spine syndrome. Abnormal glycosylation of α-dystroglycan causes Walker-Warburg syndrome (POMT1 mutation at 9q34), muscle-eye-brain disease of Santavuori (POMGnT1 mutation at 1p32), Fukuyama muscular dystrophy (FCMD mutation at 8q31-q33 and 9q31), and congenital muscular dystrophy with secondary merosin deficiency (FKRP mutation at 19q13). Glycosylation defects (dystroglycanopathies) result in defective neuroblast migration in the fetal brain and also can cause dilated cardiomyopathy. The dystroglycan molecule interacts with both proteins of the plasma (sarclemmal) membrane and those of the extracellular matrix and basal lamina not only in muscle but also in brain, where defective dystroglycan and poor glycosylation result in gaps in the pial limiting membrane, a discontinuous glia limitans, causing cobblestone lissencephaly and glioneuronal heterotopia of overmigrated neural cells during formation of the cerebral cortex.

The Fukuyama type of congenital muscular dystrophy is the second most common muscular dystrophy in Japan (after DMD); it has also been reported in children of Dutch, German, Scandinavian, and Turkish ethnic backgrounds. In the Fukuyama variety, severe cardiomyopathy and malformations of the brain usually accompany the skeletal muscle involvement. Signs and symptoms related to these organs are prominent: cardiomegaly and heart failure, intellectual disability, seizures, microcephaly, and failure to thrive.

Central neurologic disease can accompany forms of congenital muscular dystrophy other than Fukuyama disease. Mental and neurologic status is the most variable feature; an apparently normal brain and normal intelligence do not preclude the diagnosis if other manifestations indicate this myopathy. The cerebral malformations that occur are not consistently of one type and vary from severe dysplasias (holoprosencephaly, lissencephaly) to milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia). Seizures are a frequent complication, as early as the neonatal period, and may include infantile spasms and other severe infantile epilepsies.

Congenital muscular dystrophy is a constant association with cerebrodysgenesis in the Walker-Warburg syndrome and in muscle-eye-brain disease of Santavuori. The neuropathologic findings are those of neuroblast migratory abnormalities in the cerebral cortex, cerebellum, and brainstem. Studies indicate considerably more genetic overlap between Walker-Warburg, Fukuyama, and muscle-eye-brain forms of congenital muscular dystrophy that explain mixed and transitional phenotypes, so that, for example, a Fukutin-related (FKRP) gene can cause a Walker-Warburg or muscle-eye-brain presentation, or POMGnT1 also can produce phenotypes other than classic Walker-Warburg disease.

LABORATORY FINDINGS

Serum CK level is usually moderately elevated from several hundred to many thousand IU/L; only marginal increases are sometimes found. EMG shows nonspecific myopathic features. Investigation of all forms of congenital muscular dystrophy should include cardiac assessment and an imaging study of the brain. Muscle biopsy is essential for the diagnosis, but if there is a high degree of suspicion (e.g., a confirmed genetic defect in a sibling), specific genetic testing might avoid the muscle biopsy.

DIAGNOSIS

Muscle biopsy is diagnostic in the neonatal period or thereafter. An extensive proliferation of endomysial collagen envelopes individual muscle fibers even at birth, also causing them to be rounded in cross-sectional contour by acting as a rigid sleeve, especially during contraction. The perimysial connective tissue and fat are also increased, and the fascicular organization of the muscle may be disrupted by the fibrosis. Tissue cultures of intramuscular fibroblasts exhibit increased collagen synthesis, but the structure of the collagen is normal. Muscle fibers vary in diameter, and many show central nuclei, myofibrillar splitting, and other cytoarchitectural alterations. Scattered degenerating and regenerating fibers are seen. No inflammation or abnormal inclusions are found.

Immunocytochemical reactivity for merosin (α1 chain of laminin) at the sarcomemmal region is absent in approximately 40% of cases and normally expressed in the others (Figs. 609-6 and 609-7).

![Figure 609-6 Quadriceps femoris muscle biopsy of a 6 mo old girl with congenital muscular dystrophy associated with merosin (α1-laminin) deficiency. A, Histologically, the muscle is infiltrated by a great proliferation of collagenous connective tissue; myofibers vary in diameter, but necrotic fibers are rare. B, Immunocytochemical reactivity for merosin (α1-laminin) is absent in all fibers, including the intramuscular myofibers of a muscle spindle seen at bottom. C, Dystrophin expression (rod domain) is normal. Compare with Figures 609-2, 609-3, and 609-7.](image)
Merosin is a protein that binds the sarcolemmal membrane of the myofiber to the basal lamina or basement membrane. Merosin also is expressed in brain and in Schwann cells. The presence or absence of merosin does not always correlate with the severity of the myopathy or predict its course, but cases with merosin deficiency tend to have more severe cerebral involvement. Adhalin (α-dystroglycan) may be secondarily reduced in some cases. Collagen VI is selectively reduced or absent in Ullrich disease because of a mutation in the COL6A gene. Mitochondrial dysfunction may be another secondary defect.

**TREATMENT**

Only supportive therapy is available in general. Cyclosporine might correct the mitochondrial dysfunction and muscular apoptosis in collagen VI myopathy. Though no curative treatment is presently available for the congenital muscular dystrophies, a consensus statement on the standard of supportive care was issued at a special workshop in 2009 and published the following year. It covers aspects of various organ systems that could be involved, including neurologic, pulmonary, gastroenterologic, cardiac, orthopedic/rehabilitation, and palliative care.

*Bibliography is available at Expert Consult.*
Bibliography


THYROID MYOPATHIES
See also Chapters 563-568.

Thyrotoxicosis causes proximal weakness and wasting accompanied by myopathic electromyographic changes. Thyroxine binds to myofibrils and, if in excess, impairs contractile function. Hyperthyroidism can also induce myasthenia gravis and hypokalemic periodic paralysis, the latter mainly affecting East Asian males who have a genetic predisposition. Mutation in the gene KCNJ18 may be responsible for altering the potassium channel Kir2.6 in up to one third of cases. Potassium supplementation and propranolol are useful in treating thyrotoxic periodic paralysis.

Hypothyroidism, whether congenital or acquired, consistently produces hypotonia and a proximal distribution of weakness. Although muscle wasting is most characteristic, one form of cretinism, the Kocher-Debré-Sémélaigne syndrome, is characterized by generalized pseudohypertrophy of weak muscles. Infants can have a Herculean appearance reminiscent of myotonia congenita. The serum creatine kinase (CK) level is elevated in hypothyroid myopathy and returns to normal after thyroid replacement therapy.

Results of muscle biopsy in hypothyroidism reveal acute myopathic changes, including myofiber necrosis and sometimes central cores. In hyperthyroidism, the muscle biopsy specimen shows only mild, nonspecific myopathic changes without necrosis of myofibers.

The clinical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolve after appropriate treatment of the thyroid disorder. Many of the systemic symptoms of hyperthyroidism, including myopathic weakness and ophthalmoparesis, improve with the administration of β-blockers.

Most patients with primary hyperparathyroidism (see Chapter 573) develop weakness, fatigability, fasciculations, and muscle wasting that is reversible after removal of the parathyroid adenoma. The serum creatine kinase and muscle biopsy remain normal, but the electromyogram can show nonspecific myopathic features. A minority of patients develop myotonia that could be confused with myotonic dystrophy.

STEROID-INDUCED MYOPATHY
Natural Cushing disease and iatrogenic Cushing syndrome from exogenous corticosteroid administration can cause painless, symmetric, progressive proximal weakness, increased serum creatine kinase levels, and a myopathic electromyogram and muscle biopsy specimen (see Chapter 577). Myosin filaments may be selectively lost. The 9α-fluorinated steroids, such as dexamethasone, betamethasone, and triamcinolone, are the most likely to produce steroid myopathy. Dexamethasone alters the abundance of ceramides in myotubes in developing muscle. In patients with dermatomyositis or other myopathies treated with steroids, it is sometimes difficult to distinguish refractoriness of the disease from steroid-induced weakness, especially after long-term steroid administration. Vitamin D is another factor altering muscle metabolism and particularly its sensitivity to insulin; vitamin D deficiency may be accentuated and contribute to steroid myopathy, especially in type 2 diabetic patients and insulin resistance.

All patients who have been taking steroids for long periods develop reversible type II myofiber atrophy; this is a steroid effect but is not steroid myopathy unless it progresses to become a necrotizing myopathy. At greatest risk in the pediatric age group are children requiring long-term steroid therapy for asthma, rheumatoid arthritis, dermatomyositis, lupus, and other autoimmune or inflammatory diseases or who are being treated for leukemia or other hematologic diseases.
In addition to steroids, the drugs listed in Table 610-1 can cause acute or chronic toxic myopathies. An incompletely understood entity known as critical illness myopathy is a progressive weakness of patients with extended illnesses who remain in the intensive care unit; it is associated pathologically with selective loss of thick (myosin) myofilaments; immobility and excessive steroid treatment are believed to be important factors. Various steroids are sometimes used chronically in the treatment of Duchenne muscular dystrophy; they may actually exaggerate the weakness because of steroid myopathy superimposed on the dystrophic process (see Chapter 609).

Hyperaldosteronism (Conn syndrome) is accompanied by episodic and reversible weakness similar to that of periodic paralysis. The proximal myopathy can become irreversible in chronic cases. Elevated creatine kinase levels and even myoglobinuria sometimes occur during acute attacks. Arterial hypertension is a frequent manifestation and, in children, aldosterone-secreting adenomas should be considered in the differential diagnosis of idiopathic hypertension. Hereditary primary aldosteronism is due to a mutation in one of the potassium channel genes $\text{KCNJ5}$ and $\text{GIRK4}$.

Chronic growth hormone excess (sometimes illicitly acquired by adolescent athletes or seen in acromegaly) produces atrophy of some myofibers and hypertrophy of others, and scattered myofiber degeneration. Despite the augmented protein synthesis induced by growth hormone, it impairs myofibrillar adenosine triphosphatase activity and reduces sarcolemmal excitability, with resultant diminished, rather than increased, strength corresponding to the larger muscle mass. It has been used therapeutically in muscular dystrophy with both a positive effect and complications. Ghrelin is an intestinal hormone that activates a growth hormone secretagog receptor and stimulates growth hormone release. In addition to its effect as a “hunger hormone” that involves food intake and fat deposition, it also prevents muscular atrophy by inducing myodifferentiation and myoblast fusion.

Bibliography is available at Expert Consult.
Bibliography


Table 611-1 describes the differential diagnosis of metabolic myopathies.

### 611.1 Periodic Paralyses (Potassium-Related) and Other Muscle Channelopathies

Episodic, reversible weakness or paralysis, known as periodic paralysis, is associated with transient alterations in serum potassium levels, usually hypokalemia but occasionally hyperkalemia. All familial forms of periodic paralysis are caused by mutations in genes encoding voltage-gated ion channels in muscle: sodium, calcium, and potassium. Mutations in the CACNA1S voltage-gated calcium (not potassium) channel are the etiology of hypokalemic periodic paralysis. Nonhereditary causes of periodic paralysis are caused by a diverse group of disorders that affect potassium balance (Table 611-2). During

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**Table 611-1** Metabolic and Mitochondrial Myopathies

<table>
<thead>
<tr>
<th>GLYCOGEN METABOLISM DEFICIENCIES</th>
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<tr>
<td>Type II: α-1,4-Glucosidase (acid maltase)</td>
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<td>Type III: Debranching</td>
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<td>Type IV: Branching</td>
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<td>Type VII: Phosphofructokinase (Tarui disease)*</td>
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<td>Type VIII: Phosphorylase B kinase*</td>
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<td>Type IX: Phosphoglycerate kinase*</td>
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<td>Type X: Phosphoglycerate mutase*</td>
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<td>Type XI: Lactate dehydrogenase*</td>
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<td>Carnitine palmitoyltransferase*</td>
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<tr>
<td>Secondary carnitine deficiency</td>
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<tr>
<td>β-Oxidation defects</td>
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<td>Medications (valproic acid)</td>
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<td>Myoadenylate deaminase deficiency</td>
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<td>Pearson syndrome</td>
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<td>Infantile myopathy and lactic acidosis</td>
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*Deficiency can produce exercise intolerance and myoglobinuria.

attacks, myofibers are electrically unexcitable, although the contractile apparatus can respond normally to calcium. The genetic disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, epinephrine including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice. The defective genes are at the 17q13.1-13.3 locus in 

**HYPOKALEMIC**

Thyrotoxic

Primary hyperaldosteronism (Conn syndrome)

Renal tubular acidosis (e.g., Fanconi syndrome)

Juxtaglomerular apparatus hyperplasia (Bartter syndrome)

Gastrointestinal potassium wastage

Villous adenoma

Laxative abuse

Pancreatic non-insulin-secreting tumors with diarrhea

Nontropical sprue

Barium intoxication

Potassium-depleting diuretics

Amphotericin B

Licorice

Corticosteroids

Toluene toxicity

p-Aminosalicylic acid

Carbenoxolone

**HYPERKALEMIC**

Addison disease

Hypoaldosteronism

Excessive potassium supplementation

Potassium-sparing diuretics

Chronic renal failure

**Table 611-2** Secondary Causes of Periodic Paralysis

<table>
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<th>HYPOKALEMIC</th>
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<td>Addison disease</td>
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<td>Potassium-depleting diuretics</td>
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<td>Licorice</td>
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<td>Toluene toxicity</td>
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<td>p-Aminosalicylic acid</td>
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<td>Carbenoxolone</td>
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attacks, myofibers are electrically unexcitable, although the contractile apparatus can respond normally to calcium. The genetic disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, epinephrine including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice. The defective genes are at the 17q13.1-13.3 locus in **hypokalemic periodic paralysis**, the same as in paramyotonia congenita, and at the 1q31-32 locus in **hypokalemic periodic paralysis**.

Attacks often begin in infancy, particularly in the hypokalemic form, and the disease is nearly always symptomatic by 10 yr of age, affecting both sexes equally. Late childhood or adolescence is the more typical age of onset of the hypokalemic form, Andersen-Tawil syndrome, and paramyotonia congenita. Periodic paralysis is an episodic event; patients are unable to move after awakening and gradually recover muscle strength during the next few minutes or hours. All 4 extremities are involved. Muscles that remain active in sleep, such as the diaphragm, extracocular muscles (rapid eye movements), and cardiac muscle, are not affected. Patients are normal between attacks, but in adult life the attacks become more frequent, and the disorder causes progressive myopathy with permanent weakness even between attacks. The usual frequency of attacks in childhood is once a week.

Malignant hyperthermia

This syndrome is usually inherited as an autosomal dominant trait. It occurs in all patients with central core disease but is not limited to that particular myopathy. The gene is at the 19q13.1 locus in both central core disease and malignant hyperthermia without this specific myopathy. At least 15 separate mutations in this gene are associated with malignant hyperthermia. The gene programs the ryanodine receptor, a tetrameric calcium release channel in the sarcoplasmic reticulum, in apposition to the voltage-gated calcium channel of the transverse tubule. It occurs rarely in Duchenne and other muscular dystrophies, in various other myopathies, in some children with scoliosis, and in an isolated syndrome not associated with other muscle disease. Affected children sometimes have peculiar facies. All ages are affected, including premature infants whose mothers underwent general anesthesia for cesarean section.

Acute episodes are precipitated by exposure to general anesthetics and occasionally to local anesthetic drugs. Patients suddenly develop extreme fever, rigidity of muscles, and metabolic and respiratory acidosis; the serum CK level rises to as high as 35,000 IU/L. Myoglobinemia can result in tubular necrosis and acute renal failure.

The muscle biopsy specimen obtained during an episode of malignant hyperthermia is not helpful but shows widely scattered necrosis of muscle fibers known as **rhabdomyolysis**. Between attacks, the muscle biopsy specimen is normal unless there is an underlying chronic myopathy.

It is important to recognize patients at risk of malignant hyperthermia because the attacks may be prevented by administering dantrolene.
Bibliography

sodium before an anesthetic is given. Patients at risk, such as siblings, are identified by the caffeine contracture test: a portion of fresh muscle biopsy tissue in a saline bath is attached to a strain gauge and exposed to caffeine and other drugs; an abnormal spasm is diagnostic. The syndrome-associated receptor also may be demonstrated by immunohistochemistry in frozen sections of the muscle biopsy. The gene defect of the ryanodine receptor is present in 50% of patients; gene testing is available only for this genetic group. This receptor also may be seen in the muscle biopsy by immunoreactivity. Another candidate gene is at the 1q31 locus.

Apart from the genetic disorder of malignant hyperthermia, some drugs can induce acute rhabdomyolysis with myoglobinuria and potential renal failure, but this usually occurs in patients who are predisposed by some other metabolic disease (mitochondrial myopathies). Valproic acid can induce this process in children with mitochondrial cytopathies or with carnitine palmitoyltransferase deficiency.

### 611.3 Glycogenoses

**Harvey B. Sarnat**

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**Glycogenosis I** (von Gierke disease) is not a true myopathy because the deficient liver enzyme glucose-6-phosphatase is not normally present in muscle. Nevertheless, children with this disease are hypotonic and mildly weak for unknown reasons.

**Glycogenosis II** (Pompe disease) is an autosomal recessively inherited deficiency of the glycylcystic lysosomal enzyme α-glucosidase (formerly known as acid maltase) that cleaves the α-1,4 and α-1,6 glycosidic linkages. Of the 12 known glycogenoses, type II is the only one with a defective lysosomal enzyme. The defective gene is at locus 17q23, with more than 200 distinct mutations identified. Two clinical forms are described. The **infantile** form is a severe generalized myopathy and cardiomyopathy. Patients have cardiomegaly and hepatomegaly and are diffusely hypotonic and weak. The serum CK level is greatly elevated. A muscle biopsy specimen reveals a vacuolar myopathy with abnormal lysosomal enzymatic activities such as acid and alkaline phosphatases. Evidence of a secondary mitochondrial cytopathy is often demonstrated; it includes electron microscopic demonstration of paracrystallin structures within muscle mitochondria and low concentrations of respiratory chain enzymes. Death in infancy or early childhood is usual; however, enzyme replacement therapy has improved the outcome.

The **late childhood or adult** form is a much milder myopathy without cardiac or hepatic enlargement. It might not become clinically expressed until later childhood or early adult life but may be symptomatic as myopathic weakness and hypotonia even in early infancy. Even in late adult-onset acid maltase deficiency, 50% of the patients report difficulties with muscle strength dating from childhood. Ultrastructural evidence of secondary mitochondrial cytopathy also occurs, as with infantile Pompe disease. MRI of muscle may show distinctive changes that differ from other myopathies.

The serum CK level is greatly elevated, and the muscle biopsy findings are diagnostic even in the presymptomatic stage. The diagnosis of glycogenosis II is confirmed by quantitative assay of acid maltase activity in muscle or liver biopsy specimens. A rare variant of the mild form of acid maltase deficiency can show muscle acid maltase activity in the low normal range with only intermittent decreases to subnormal values; the muscle biopsy findings are similar although milder. In another form, **Danon disease**, transmitted as an X-linked recessive trait at the Xq24 locus, the primary deficiency is lysosomal membrane protein-2 (LAMP2) and results in hypertrophic cardiomyopathy, proximal myopathy, and intellectual disability.

**Glycogenosis III** (Cori-Forbes disease), a deficiency of debrancher enzyme (amylo-1,6-glucosidase), is more common than is usually diagnosed, and it is generally the least severe. Hypotonia, weakness, hepatomegaly, and fasting hypoglycemia in infancy are common, but these features often resolve spontaneously, and patients become asymptomatic in childhood and adult life. Others experience slowly progressive distal muscle wasting, hepatic cirrhosis, recurrent hypoglycemia, and heart failure. This more serious chronic course is particularly seen in the Inuit population. Minor myopathic findings including vacuolation of muscle fibers are found in the muscle biopsy specimen.

**Glycogenosis IV** (Andersen disease) is a deficiency of brancher enzyme, resulting in the formation of an abnormal glycogen molecule, amylolipin, in the liver, reticuloendothelial cells, and skeletal and cardiac muscle. Hypotonia, generalized weakness, muscle wasting, and contractures are the usual signs of myopathic involvement. Most patients die before age 4 yr because of hepatic or cardiac failure. A few children without neuromuscular manifestations have been described.

**Glycogenosis V** (McArdle disease) is caused by muscle glycogen phosphorylase deficiency inherited as an autosomal recessive trait at locus 11q13, encoded by the PMGM gene. Exercise intolerance is the cardinal clinical feature. Physical exertion results in cramps, weakness, and myoglobinuria, but strength is normal between attacks. The serum CK level is elevated only during exercise. A characteristic clinical feature is lack of the normal rise in serum lactate levels during ischemic exercise because of inability to convert pyruvate to lactate under anaerobic conditions in vivo. Myophosphorylase deficiency may be demonstrated histochemically and biochemically in the muscle biopsy tissue. Some patients have a defect in adenosine monophosphate–dependent muscle phosphorylase β-kinase, a phosphorylase enzyme activator. Muscle phosphorylase deficiency was the first neuromuscular disease to be diagnosed by MR spectroscopy, which shows that the intramuscular pH does not decrease with exercise and there is no depletion of adenosine triphosphatase but that the phosphocreatine concentration falls excessively. This noninvasive technique may be useful in some patients if the radiologist is experienced with the disease.

A rare **neonatal form of myophosphorylase deficiency** causes feeding difficulties in early infancy, may be severe enough to result in neonatal death, or can follow a course of slowly progressive weakness resembling a muscular dystrophy. The long-term prognosis is good. Patients must learn to moderate their physical activities, but they do not develop severe chronic myopathic handicaps or cardiac involvement.

**Glycogenosis VII** (Tariu disease) is muscle phosphofructokinase deficiency. Although this disease is rarer than glycogenosis V, the symptoms of exercise intolerance, clinical course, and inability to convert pyruvate to lactate are identical. The distinction is made by biochemical study of the muscle biopsy specimen. It is transmitted as an autosomal recessive trait at the 1cenq32 locus and some mutations are particularly prevalent in the Ashkenazi Jewish population.

**Bibliography is available at Expert Consult.**

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### 611.4 Mitochondrial Myopathies

**Harvey B. Sarnat**

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Several diseases involving muscle, brain, and other organs are associated with structural and functional abnormalities of mitochondria, producing defects in aerobic cellular metabolism, the electron transport chain, and the Krebs cycle. Because mitochondria are found in all cells, except mature erythrocytes, the term **mitochondrial cytopathy** is used preferentially to emphasize the multisystemic nature of these diseases. The structural aberrations are best demonstrated by electron microscopy of the muscle biopsy sample, revealing a proliferation of abnormally shaped cristae, including stacked or whorled cristae and paracrystallin structures that occupy the space between cristae and are formed from CK. Muscle biopsies of neonates, infants, and toddlers show more severe involvement of endothelial cells of intramuscular capillaries than of myofibers, unlike the reverse in adults, but endothelial paracrystallin structures are globular rather than brick shaped as in myofibers. The endoplasmic reticulum becomes abnormally adherent to mitochondria. Similar endothelial mitochondrial alterations are seen in brain in Leigh and other infantile mitochondrial encephalopathies. Histochemical study of the muscle biopsy specimen reveals abnormal clumping of oxidative enzymatic activity and scattered myofibers, with
Bibliography

loss of cytochrome-c oxidase activity and with increased neutral lipids within myofibers. Ragged red muscle fibers occur in some mitochondrial myopathies, particularly those with a combination of respiratory chain complexes I and IV deficiencies. Accumulations of this membranous material beneath the muscle fiber membrane are best demonstrated by special stains, such as modified Gomori trichrome.

These characteristic histochemical and ultrastructural changes are most consistently seen with point mutations in mitochondrial transfer RNA. The large mitochondrial DNA (mtDNA) deletions of 5 or 7.4 kb (the single mitochondrial chromosome has 16.5 kb) are associated with defects in mitochondrial respiratory oxidative enzyme complexes, if as few as 2% of the mitochondria are affected, but minimal or no morphologic or histochemical changes may be noted in the muscle biopsy specimen, even by electron microscopy; hence, quantitative biochemical studies of the muscle tissue are needed to confirm the diagnosis. Because most of the subunits of the respiratory chain complexes are encoded by nuclear DNA (nDNA) rather than mtDNA, mendelian autosomal inheritance is possible, rather than maternal transmission as with pure mtDNA point mutations. Complex II (succinate dehydrogenase) is the only enzyme complex in which all of its subunits are encoded by nDNA; hence it is histochemically reactive in all mitochondrial diseases with mtDNA point mutations. Serum lactate is elevated in some diseases, and cerebrospinal fluid lactate is more consistently elevated, even if serum concentrations are normal.

Several distinct mitochondrial diseases that primarily affect striated muscle or muscle and brain are identified. These can be divided into the ragged red fiber diseases and non–ragged red fiber diseases. The ragged red fiber diseases include Kearns-Sayre, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) syndrome, MERRF (myoclonic epilepsy with ragged red fibers) syndrome, and progressive external ophthalmoplegia syndromes, which are associated with a combined defect in respiratory chain complexes I and IV. The non–ragged red fiber diseases include Leigh encephalopathy and Leber hereditary optic atrophy; they involve complex I or IV alone or, in children, the common combination of defective complexes III and V.

Kearns-Sayre syndrome is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and onset before age 20 yr. Heart block, cerebellar deficits, and high cerebrospinal fluid protein content are often associated. Visual evoked potentials are abnormal. Patients usually do not experience weakness of the trunk or extremities or dysphagia. Most cases are sporadic.

Chronic progressive external ophthalmoplegia may be isolated or accompanied by limb muscle weakness, dysphagia, and dysarthria. A few patients described as having ophthalmoplegia plus have additional central nervous system involvement. Autosomal dominant inheritance is found in some pedigrees, but most cases are sporadic.

MERRF and MELAS syndromes are other mitochondrial disorders affecting children. The latter is characterized by stunted growth, episodic vomiting, seizures, and recurring cerebral insults causing hemiparesis, hemianopia, or even cortical blindness, and dementia. The disease behaves as a degenerative disorder, and children die within a few years.

Other “degenerative” diseases of the central nervous system that also involve myopathy with mitochondrial abnormalities include Leigh subacute necrotizing encephalopathy (see Chapter 87.4) and cerebrohepatorenal (Zellweger) disease, primarily a peroxisomal disease with secondary mitochondrial alterations (see Chapter 86.2). Another recognized mitochondrial myopathy is cytochrome-c oxidase deficiency. Oculopharyngeal muscular dystrophy is also fundamentally a mitochondrial myopathy.

Mitochondrial depletion syndrome of early infancy is characterized by severely decreased oxidative enzymatic activities in most or all 5 of the complexes; in addition to diffuse muscle weakness, neonates and young infants can show multisystemic involvement and the syndrome occurs in several forms: myopathic; encephalomyopathic; hepatoencephalopathic; and intestinal encephalopathic. Cardiomyopathy and sometimes bullous skin lesions or generalized edema also can occur. Alpers syndrome is genetically homogeneous and is caused by mtDNA depletion and mutations in the POLG1 gene. Several other genes are identified, mostly in later-onset forms; hence mitochondrial depletion is a syndrome and not a single disease. Barth syndrome is an X-linked recessive mitochondrial disorder characterized by cardiomyopathy, myopathy of striated muscle, growth retardation, neutropenia, and high serum and urinary concentrations of 3-methylglutaconic acid.

Many rare diseases with only a few case reports are suspected of being mitochondrial disorders. It is also now recognized that secondary mitochondrial defects occur in a wide range of nonmitochondrial diseases, including inflammatory autoimmune myopathies, Pompe disease, and some cerebral malformations, and also may be induced by certain drugs and toxins, so that interpretation of mitochondrial abnormalities as primary defects must be approached with caution.

mtDNA is distinct from the DNA of the cell nucleus and is inherited exclusively from the mother; mitochondria are present in the cytoplasm of the ovum but not in the head of the sperm, the only part that enters the ovum at fertilization. The rate of mutation of mtDNA is 10 times higher than that of nDNA. The mitochondrial respiratory enzyme complexes each have subunits encoded either in mtDNA or nDNA. Complex II (succinate dehydrogenase, a Krebs cycle enzyme) has 4 subunits, all encoded in nDNA; complex III (ubiquinol or cytochrome-b oxidase) has 9 subunits, only 1 of which is encoded by mtDNA and 8 of which are programmed by nDNA; complex IV (cytochrome-c oxidase) has 13 subunits, only 3 of which are encoded by mtDNA. For this reason, mitochondrial diseases of muscle may be transmitted as autosomal recessive traits rather than by strict maternal transmission, even though all mitochondria are inherited from the mother.

In Kearns-Sayre syndrome, a single large mtDNA deletion has been identified; but other genetic variants are known; in MERRF and MELAS syndromes of mitochondrial myopathy, point mutations occur in transfer RNA.

INVESTIGATIONS

Investigation for mitochondrial cytopathies begins with serum lactate. Lactic acid is not increased in all mitochondrial cytopathies, so that a normal result is not necessarily reassuring; cerebrospinal fluid lactate is increased in some cases in which serum lactate is normal, particularly if there are clinical signs of encephalopathy. Serum 3-methylglutaconic acid often is increased in mitochondrial cytopathies in general, demonstrated in more than 50 different genetic mutations, and hence is a good screening measurement; it rarely is increased in other metabolic diseases. This product also may be increased in urine. Hepatic enzymes (transaminases) should be measured in blood. Cardiac evaluation often is warranted. Molecular markers in blood for the common diseases with known mtDNA point mutations identify many of the mitochondrial cytopathies presenting in adult life or adolescence, but less frequently in children and least in young infants. MRI of the brain may reveal hypertensive lesions of the basal ganglia and MR spectroscopy can demonstrate an increased lactate peak. The muscle biopsy provides the best evidence of all mitochondrial myopathies and should include histochemistry for oxidative enzymes, electron microscopy, and quantitative biochemical assay of respiratory chain enzyme complexes and coenzyme-Q10; muscle tissue also can be analyzed for mtDNA. Many mitochondrial disorders also can affect the Schwann cells and axons of peripheral nerves and present clinically with neuropathy; hence motor and sensory nerve conduction velocities can be measured in selected patients; sural nerve biopsy is required only rarely if neuropathy is the predominant finding and the diagnosis is not evident from other studies.

TREATMENT

There is no effective treatment of mitochondrial cytopathies, but various “cocktails” are often used empirically to try to overcome the metabolic deficits. These include oral carnitine supplements, riboflavin, coenzyme-Q10, ascorbic acid (vitamin C), vitamin E, and other antioxidants. Although some anecdotal reports are encouraging, no controlled studies that prove efficacy have been published.

Bibliography is available at Expert Consult.
Bibliography


611.5 Lipid Myopathies

Harvey B. Sarnat

See Chapter 86.4.

Considered as metabolic organs, skeletal muscles are the most important sites in the body for long-chain fatty acid metabolism because of their large mass and their rich density of mitochondria where fatty acids are metabolized. They are the major source of energy for skeletal muscle during sustained exercise or fasting. Hereditary disorders of lipid metabolism that cause progressive myopathy are an important, relatively common, and often treatable group of muscle diseases. Increased lipid within myofibers is seen in the muscle biopsy of some mitochondrial myopathies and is a constant, rather than an unpredictable, feature of specific diseases. Among the ragged red fiber diseases, Kearns-Sayre syndrome always shows increased neutral lipid, whereas MERRF and MELAS syndromes do not, a useful diagnostic marker for the pathologist. Free fatty acids are converted to acyl-coenzyme A by fatty acyl-coenzyme A synthetases; the resulting long-chain fatty acids bind to carnitine and are transported into mitochondria where β-oxidation is carried out. Disorders of lipid fuel utilization and lipid storage disorders can be divided into defects of transport and oxidation of exogenous fatty acids within mitochondria and defects of endogenous triglyceride catabolism.

Muscle carnitine deficiency is an autosomal recessive disease caused by mutations in the SLC22A5 gene, involving deficient transport of dietary carnitine across the intestinal mucosa. Carnitine is acquired from dietary sources but is also synthesized in the liver and kidneys from lysine and methionine; it is the obligatory carrier of long- and medium-chain fatty acids into muscle mitochondria.

The clinical course may be one of sudden exacerbations of weakness or can resemble a progressive muscular dystrophy with generalized proximal myopathy and sometimes facial, pharyngeal, and cardiac involvement. Symptoms usually begin in late childhood or adolescence and may be delayed until adult life. Progression is slow but can end in death.

Serum CK level is mildly elevated. Muscle biopsy material shows vacuoles filled with lipid within muscle fibers in addition to nonspecific changes suggestive of a muscular dystrophy. Mitochondria can appear normal or abnormal. Carnitine measured in muscle biopsy tissue is reduced, but the serum carnitine level is normal.

Treatment stops the progression of the disease and can even restore lost strength if the disease is not too advanced. It consists of special diets low in long-chain fatty acids. Steroids can enhance fatty acid transport. Specific therapy with l-carnitine taken orally in large doses overrides the intestinal barrier in some patients. Some patients also improve when given supplementary riboflavin, and other patients seem to improve with propranolol.

Systemic carnitine deficiency is a disease of impaired renal and hepatic synthesis of carnitine rather than a primary myopathy. Patients with this autosomal recessive disease experience progressive proximal myopathy and show muscle biopsy changes similar to those of muscle carnitine deficiency; however, the onset of weakness is earlier and may be evident at birth. Endocardial fibroelastosis also can occur. Episodes of acute hepatic encephalopathy resembling Reye syndrome can occur. Hypoglycemia and metabolic acidosis complicate acute episodes. Cardiomyopathy may be the predominating feature in some cases and result in death.

Cerebral infarctions and myopathy occur in children, particularly when accompanied by hypoglycemia. Mean age at presentation is approximately 9 yr. Brain MRI shows distinctive changes related to multiple infarcts of various sizes.

The concentration of carnitine is reduced in serum as well as in muscle and liver. l-Carnitine deficiency can be corrected by oral administration of carnitine on a daily basis.

A similar clinical syndrome may be a complication of renal Fanconi syndrome because of excessive urinary loss of carnitine or loss during chronic hemodialysis.

611.6 Vitamin E Deficiency Myopathy

Harvey B. Sarnat

In experimental animals, deficiency of vitamin E (α-tocopherol, an antioxidant also important in mitochondrial superoxide generation) produces a progressive myopathy closely resembling a muscular dystrophy. Myopathy and neuropathy are recognized in humans who lack adequate intake of this antioxidant. Patients with chronic malabsorption, those undergoing long-term dialysis, and premature infants who do not receive vitamin E supplements are particularly vulnerable. Treatment with high doses of vitamin E can reverse the deficiency. Myopathy caused by chronic hypervitaminosis E also occurs.

Bibliography is available at Expert Consult.
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Bibliography
Myasthenia Gravis

Autoimmune Myasthenia Gravis

Myasthenia gravis is a chronic autoimmune disease of neuromuscular blockade, characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing. It must be distinguished from congenital myasthenic...
syndrome, a genetic disorder of receptors on the postsynaptic membrane of the neuromuscular junction and toxin-induced myasthenia, such as botulism (see below). The release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane (i.e., sarcolemma) or motor end plate is less responsive than normal. A decreased number of available ACh receptors is a result of circulating receptor-binding antibodies in most cases of autoimmune myasthenia.

A rare familial myasthenia gravis is an autosomal recessive trait not associated with increased plasma anti-ACh antibodies. One familial form is a deficiency of motor end plate acetylcholinesterase (AChE). Most congenital (familial) forms are postsynaptic defects. Infants born to myasthenic mothers can have a transient neonatal myasthenic syndrome secondary to placentally transferred anti-ACh receptor antibodies, distinct from congenital myasthenic syndromes (Tables 612-1 and 612-2).

Clinical Manifestations
In juvenile autoimmune myasthenia gravis, unilateral or bilateral but usually asymmetrical ptosis and some degree of extraocular muscle weakness are the earliest and most constant signs. Extraocular weakness is not confined to muscles innervated by just 1 or 2 of the 3 corresponding brainstem nuclei and is progressive. Older children might complain of diplopia, and young children might hold open their eyes with their fingers or thumbs if the ptosis is severe.

Table 612-1 Classification of the Congenital Myasthenic Syndromes

<table>
<thead>
<tr>
<th>PRESYNAPTIC DEFECTS</th>
<th>SYNAPTIC DEFECTS</th>
<th>POSTSYNAPTIC DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paucity of synaptic vesicles and decreased quantal release</td>
<td>End plate acetylcholinesterase deficiency</td>
<td></td>
</tr>
<tr>
<td>Congenital myasthenic syndromes with episodic apnea (choline acetyltransferase deficiency)</td>
<td>Primary acetylcholine receptor deficiency</td>
<td></td>
</tr>
<tr>
<td>Lambert-Eaton syndrome–like form</td>
<td>Reduced receptor expression as a result of acetylcholine receptor mutations</td>
<td></td>
</tr>
<tr>
<td>Acetylcholine receptor antagonist</td>
<td>Reduced receptor expression because of rapyn mutations</td>
<td></td>
</tr>
<tr>
<td>DOK7 mutations</td>
<td>Primary acetylcholine receptor kinetic abnormality with or without acetylcholine receptor deficiency</td>
<td></td>
</tr>
</tbody>
</table>


Table 612-2 Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndromes

<table>
<thead>
<tr>
<th>Presynaptic</th>
<th>Synaptic</th>
<th>Postsynaptic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLINE ACETYLTRANSFERASE DEFICIENCY</td>
<td>LEMS-LIKE FORM</td>
<td>AChE DEFICIENCY</td>
</tr>
<tr>
<td>Autosomal dominant inheritance</td>
<td>X (most mutations)</td>
<td></td>
</tr>
<tr>
<td>Episodic apnea triggered by stressors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neonatal hypotonia and respiratory insufficiency</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Skeletal deformities</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Delayed pupillary light responses</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prominent neck, wrist, and finger extensor weakness</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Repetitive CMAPs after single stimulus</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Progressive decrement with prolonged exercise or repetitive stimulation</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Marked increment (&gt;200%) with high-frequency repetitive stimulation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Decrement repairs with AChE inhibitors</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical improvement with AChE inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical worsening with AChE inhibitors</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAPs, compound muscle action potentials; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

enough to obstruct vision. Pupillary responses to light are preserved. Dysphagia and facial weakness also are common and, in early infancy, feeding difficulties are frequent as the cardinal sign of myasthenia; in severe cases, aspiration and airway obstruction may occur. Poor head control because of weakness of the neck flexors may be prominent. Involvement initially may appear to be limited to bulbar-innervated muscles, but the disease is systemic and progressive weakness eventually involves limb-girdle muscles and distal muscles of the hands in most cases. Fasciculations of muscle, myalgias, and sensory symptoms do not occur. Tendon stretch reflexes may be diminished but rarely are lost. Ocular myasthenia gravis may prove to be transitory over time, but in some patients weakness never progresses to involve axial or appendicular muscles. This group accounts for approximately 25\% of all juvenile myasthenia gravis patients and is most frequent in children of Chinese and southeastern Asian descent, suggesting an ethnic genetic predisposition.

Rapid fatigue of muscles is a characteristic feature of myasthenia gravis that distinguishes it from most other neuromuscular diseases. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30–90 sec. Holding the head up from the surface of the examining table while lying supine is very difficult, and gravity cannot be overcome for more than a few seconds. Repetitive opening and closing of the fists produces rapid fatigue of hand muscles, and patients cannot elevate their arms for more than 1–2 min because of fatigue of the deltoids. Patients are more symptomatic late in the day or when tired. Dysphagia can interfere with eating, and the muscles of the jaw soon tire when an affected child chews. Reviewing activities of daily living helps determine the severity of symptoms (Table 612-3).

Myasthenic crisis is an acute or subacute severe increase in weakness in patients with myasthenia gravis, usually precipitated by an intercurrent infection, surgery, or even emotional stress. It may require intravenous cholinesterase inhibitors, immunoglobulin, plasma exchange, gavage feeding, and even transitory ventilator support. It must be distinguished from cholinergic crisis secondary to overdosing with anticholinesterase medications. The muscarinic effects include abdominal cramps, diarrhea, profuse sweating, salivation, bradycardia, increased weakness, and miosis. Cholinergic crisis requires only supportive care and withholding of further doses of cholinergic drugs, and it passes within a few hours; the dose of medication to be restarted should be reconsidered, unless the patient had taken an overdose that was not prescribed.

Approximately 30\% of affected adolescents show elevations, but anti-AChR antibodies are only occasionally demonstrated in the plasma of prepubertal children. Some with negative titers of AChE exhibit anti–muscle-specific tyrosine kinase (MuSK) circulating antibodies. MuSK is localized at the neuromuscular junction and appears essential to fetal development of this junction. MuSK myasthenia usually occurs in female infants and toddlers and severe bulbar involvement with dysphagia is frequent, but clinical features alone cannot distinguish between these 2 different antibody forms of the disease.

Infants born to myasthenic mothers can have respiratory insufficiency, inability to suck or swallow, and generalized hypotonia and weakness. They might show little spontaneous motor activity for several days to weeks. Some require ventilatory support and feeding by gavage during this period. After the abnormal antibodies disappear from the blood and muscle tissue, these infants regain normal strength and are not at increased risk of developing myasthenia gravis in later childhood. A small minority develop fetal akinesia sequence with multiple joint contractures (arthrogryposis) that develop in utero from lack of fetal movement. AChR antibodies can usually be demonstrated in maternal blood, but at times maternal antibodies may not be detected.

### CONGENITAL MYASTHENIC SYNDROMES

A heterogeneous group of genetic diseases of neuromuscular transmission is collectively called congenital myasthenic syndromes. The etiology and pathogenesis of these syndromes are unrelated to either transitory neonatal myasthenia caused by placental transfer of maternal antibodies or to autoimmune myasthenia gravis, despite overlap of clinical symptoms. Congenital myasthenic syndromes are nearly always permanent static disorders without spontaneous remission (see Tables 612-1 and 612-2). Several distinct genetic forms are recognized, all with onset at birth or in early infancy with hypotonia, external ophthalmoplegia, ptosis, dysphagia, weak cry, facial weakness, easy muscle fatigue generally, and sometimes respiratory insufficiency or failure, the last often precipitated by a minor respiratory infection. Cholinesterase inhibitors have a favorable effect in most, but in some forms the symptoms and signs are actually worsened. Most congenital myasthenic syndromes are transmitted as autosomal recessive traits, but the slow channel syndrome is autosomal dominant.

Mutations responsible for congenital myasthenic syndromes have been identified in 18 different genes. The genetic mutations are known in less than half of children with congenital myasthenic syndromes. Of

<table>
<thead>
<tr>
<th>GRADE</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talking</td>
<td>Normal</td>
<td>Intermittent slurring or nasal speech</td>
<td>Constant slurring or nasal, but can be understood</td>
<td>Difficult to understand speech</td>
</tr>
<tr>
<td>Chewing</td>
<td>Normal</td>
<td>Fatigue with solid food</td>
<td>Fatigue with soft food</td>
<td>Gastric tube</td>
</tr>
<tr>
<td>Swallowing</td>
<td>Normal</td>
<td>Rare episode of choking</td>
<td>Frequent choking, necessitating changes in diet</td>
<td>Gastric tube</td>
</tr>
<tr>
<td>Breathing</td>
<td>Normal</td>
<td>Shortness of breath with exertion</td>
<td>Shortness of breath at rest</td>
<td>Ventilator dependence</td>
</tr>
<tr>
<td>Impairment of ability to brush teeth or comb hair</td>
<td>None</td>
<td>Extra effort, but no rest periods needed</td>
<td>Rest periods needed</td>
<td>Cannot do 1 of these functions</td>
</tr>
<tr>
<td>Impairment of ability to arise from a chair</td>
<td>None</td>
<td>Mild, sometimes uses arms</td>
<td>Moderate, always uses arms</td>
<td>Severe, requires assistance</td>
</tr>
<tr>
<td>Double vision</td>
<td>None</td>
<td>Occurs, but not daily</td>
<td>Daily, but not constant</td>
<td>Constant</td>
</tr>
<tr>
<td>Eyelid droop</td>
<td>None</td>
<td>Occurs, but not daily</td>
<td>Daily, but not constant</td>
<td>Constant</td>
</tr>
</tbody>
</table>

**Table 612-3** Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

known genetic defects, rapsyn and downstream-of-kinase-7 (DOK7) are demonstrated in 85% of cases. Acetylcholine receptor deficiencies have more than 60 identified genetic mutations. Basal lamina–associated synaptic defects from mutations of the COLQ gene that encodes the collagen tail of AChR account for another 10% of cases. Another 5% of cases are presynaptic, attributed to mutations in ChAT, encoding choline acetyltransferase. Anti-AChR and anti-MuSK antibodies are usually, but not always, absent in serum, unlike in autoimmune forms of myasthenia gravis affecting older children and adults.

Three presynaptic congenital myasthenic syndromes are recognized, all as autosomal recessive traits; some of these have anti-MuSK antibodies. These children exhibit weakness of extraocular, pharyngeal, and respiratory muscles and later show girdle weakness as well. Episodic apnea is a problem in congenital myasthenia gravis. Another synaptic form is caused by congenital absence or marked deficiency of motor end plate AChE in the synaptic basal lamina; this was the first form recognized as caused by an enzymatic deficiency at the neuromuscular junction. Postsynaptic forms of congenital myasthenia are caused by mutations in ACh receptor subunit genes that alter the synaptic response to ACh. An abnormality of the ACh receptor channels appearing as high conductance and excessively fast closure may be the result of a point mutation in a subunit of the receptor affecting a single amino acid residue. Children with congenital myasthenia gravis do not experience myasthenic crises and rarely exhibit elevations of anti-ACh antibodies in plasma.

RARE OTHER CAUSES OF MYASTHENIA

Myasthenia gravis is occasionally associated with hypothyroidism, usually as caused by Hashimoto thyroiditis. Other collagen vascular diseases may also be associated with myasthenia gravis. Thymomas, noted in some adults, rarely coexist with myasthenia gravis in children, nor do carcinomas of the lung occur, which produce a unique form of myasthenia in adults called Eaton-Lambert syndrome. The Eaton-Lambert syndrome in children is rare but is reported with lymphoproliferative disorders and with neuroblastoma. Postinfectious myasthenia gravis in children is transitory and usually follows a varicella-zoster infection by 2-5 wk as an immune response.

Laboratory Findings and Diagnosis

Myasthenia gravis is one of the few neuromuscular diseases in which electromyography (EMG) is more specifically diagnostic than a muscle biopsy. A decremental response is seen to repetitive nerve stimulation; the muscle potentials diminish rapidly in amplitude until the muscle becomes refractory to further stimulation. Motor nerve conduction velocity remains normal. This unique EMG pattern is the electrophysiologic correlate of the fatigable weakness observed clinically and is reversed after a cholinesterase inhibitor is administered. A myasthenic decrement may be absent or difficult to demonstrate in muscles that are not involved clinically. This feature may be confusing in early cases or in patients showing only weakness of extracranial muscles. Microelectrode studies of end plate potentials and currents reveal whether the transmission defect is presynaptic or postsynaptic. Special electrophysiologic studies are required in the classification of congenital myasthenic syndromes and involve estimating the number of ACh receptors per end plate and in vitro study of end plate function. These special studies and patch-clamp recordings of kinetic properties of channels are performed on special biopsy samples of intercostal muscle strips that include both origin and insertion of the muscle but are only performed in specialized centers. If myasthenia is limited to the extraocular, levator palpebrae, and pharyngeal muscles, evoked-potential EMG of the muscles of the extremities and spine, diagnostic in the generalized disease, usually is normal.

Anti-AChR antibodies should be assayed in the plasma but are inconsistently demonstrated. Antibodies against the MuSK receptor should be sought in children without circulating AChR antibodies, a diagnostic finding when elevated, which further delineates the etiology. Many cases of congenital myasthenia gravis result from failure to synthesize or release ACh at the presynaptic membrane. In some cases, the gene that mediates the enzyme choline acetyltransferase for the synthesis of ACh is mutated. In others, there is a defect in the quantal release of vesicles containing ACh. The treatment of such patients with cholinesterase inhibitors is futile. Assays of anti-rapsyn, anti-Dok7, COLQ, and ChAT antibodies are available in a few specialized laboratories.

Other serologic tests of autoimmune disease, such as antinuclear antibodies and abnormal immune complexes, should also be sought. If these are positive, more extensive autoimmune disease involving vasculitis or tissues other than muscle is likely. A thyroid profile should always be examined. The serum creatine kinase level is normal in myasthenia gravis.

The heart is not involved, and electrocardiographic findings remain normal. Radiographs of the chest often reveal an enlarged thymus, but the hypertrophy is not a thymoma. It may be further defined by tomography or by CT or MRI of the anterior mediastinum if the radiographic findings are uncertain, but these imaging modalities are not recommended routinely because of radiation exposure and anesthetic risk, which is higher in myasthenic patients than in normal children.

The role of conventional muscle biopsy in myasthenia gravis is limited. It is not required in most cases, but approximately 17% of patients show inflammatory changes, sometimes called lymphohorraghes, that are interpreted by some physicians as a mixed myasthenia-polymyositis immune disorder. Muscle biopsy tissue in myasthenia gravis shows nonspecific type II muscle fiber atrophy, similar to that seen with disuse atrophy, steroid effects on muscle, polymyalgia rheumatica, and many other conditions. The ultrastructure of motor end plates shows simplification of the membrane folds; the ACh receptors are located in these postsynaptic folds, as shown by bungarotoxsin (snake venom), which binds specifically to the ACh receptors.

A clinical test for myasthenia gravis is administration of a short-acting cholinesterase inhibitor, usually edrophonium chloride. Ptosis and ophthalmoplegia improve within a few seconds, and fatigability of other muscles decreases.

Recommendations on the Use of Cholinesterase Inhibitors as a Diagnostic Test for Myasthenia Gravis in Infants and Children

Children 2 Yr and Older

◆ The child should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, or inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits is not a criterion.

◆ An IV infusion should be started to enable the administration of medications in the event of an adverse reaction.

◆ Electrocardiographic monitoring is recommended during the test.

◆ A dose of atropine sulfate (0.01 mg/kg) should be available in a syringe, ready for IV administration at the bedside during the edrophonium test, to block acute muscarinic effects of the cholinesterase inhibitor, mainly abdominal cramps and/or sudden diarrhea from increased peristalsis, profuse bronchotracheal secretions that can obstruct the airway, or, rarely, cardiac arrhythmias. Some physicians treat all patients with atropine before administering edrophonium, but this is not recommended unless there is a history of reaction to tests. Atropine can cause the pupils to be dilated and fixed for as long as 14 days after a single dose, and the pupillary effects of homatropine can last 4-7 days.

◆ Edrophonium chloride (Tension) is administered IV. Initially, a test dose of 0.01 mg/kg is given to ensure that the patient does not have an allergic reaction or is otherwise very sensitive to muscarinic side effects. In children weighing <30 kg, 0.1 mg/kg is the maximum total delivered dose; in children weighing >30 kg, the total delivered dose is 0.2 mg/kg. After the test dose, an intravenous injection of 0.01-0.02 mg is administered every 30-45 sec, as long as dosing does not exceed the recommended maximum dose. In adults, the average edrophonium dose to show positive responses is approximately 3.3 mg for ptosis and
approximately 2.6 mg for oculomotor symptoms. Side effects include nausea and emesis; light-headedness from bradycardia (atropine is the antidote) and bronchospasm are less common side effects. These doses may be given IM or subcutaneously, but these routes are not recommended because the results are much more variable owing to unpredictable absorption, and the test may be ambiguous or falsely negative.

- Effects should be seen within 10 sec and disappear within 120 sec. Weakness is measured as, for example, distance between upper and lower eyelids before and after administration, degree of external ophthalmoplegia, or ability to swallow a sip of water.

- Long-acting cholinesterase inhibitors, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness. The Prostigmin test may be used (as outlined later) but might not be as definitively diagnostic as the edrophonium test.

**For Children Younger Than 2 Yr**

- Infants ideally should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, and inability of cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits makes it less easy to assess results but may be a criterion at times.

- An IV infusion should be started as a rapid route for medications in the event of an adverse effect of the test medication.

- Electrocardiographic monitoring is recommended during the test.

- Pretreatment with atropine sulfate to block the muscarinic effects of the test medication is not recommended, but atropine sulfate should be available at the bedside in a prepared syringe. If needed, it should be administered IV in a dose of 0.01 mg/kg.

- Edrophonium is not recommended for use in infants; its effect is too brief for objective assessment and an increased incidence of acute cardiac arrhythmias is reported in infants, especially neonates, with this drug.

- Prostigmin methylsulfate (neostigmine) is administered IM at a dose of 0.04 mg/kg. If the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hr after the first dose (a typical dose is 0.5–1.5 mg). The peak effect is seen in 20–40 min. IV Prostigmin is contraindicated because of the risk of cardiac arrhythmias, including fatal ventricular fibrillation, especially in young infants.

- Long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness because onset and duration are less predictable.

The test should be performed in the emergency department, hospital ward, or intensive care unit; the important issue is preparation for potential complications such as cardiac arrhythmia or cholinergic crisis, as outlined.

**Treatment**

Some patients with mild myasthenia gravis require no treatment. Neostigmine methylsulfate (0.04 mg/kg) may be given IM every 4-6 hr, but most patients tolerate oral neostigmine bromide, 0.4 mg/kg every 4-6 hr. If dysphagia is a major problem, the drug should be given approximately 30 min before meals to improve swallowing. Pyridostigmine is an alternative; the dose required is approximately 4 times greater than that of neostigmine, but it may be slightly longer acting. Overdoses of cholinesterase inhibitors produce cholinergic crises; atropine blocks the muscarinic effects but does not block the nicotinic effects that produce additional skeletal muscle weakness. In the rare familial myasthenia gravis caused by absence of end plate AChE, cholinesterase inhibitors are not helpful and often cause increased weakness; these patients can be treated with ephedrine or dexamethasone, both of which increase ACh release from terminal axons.

Because of the autoimmune basis of the disease, long-term steroid treatment with prednisone may be effective. Thymectomy should be considered and might provide a cure. Thymectomy is most effective in patients who have high titers of anti-ACh receptor antibodies in the plasma and who have been symptomatic for <2 yr. Thymectomy is ineffective in congenital and familial forms of myasthenia gravis. Treatment of hypothyroidism usually abolishes an associated myasthenia without the use of cholinesterase inhibitors or steroids.

If the specific genetic mutation can be identified in a patient with one of the congenital myasthenic syndromes, specific therapeutic approaches are available for some that differ from the treatments listed above; these are well outlined by Eyemard et al (2013).

**Plasmapheresis** is effective treatment in some children, particularly those who do not respond to steroids, but plasma exchange therapy provides only temporary remission. IV immunoglobulin is beneficial and should be tried before plasmapheresis because it is less invasive. Plasmapheresis and IV immunoglobulin appear to be most effective in patients with high circulating levels of anti-ACh receptor antibodies. Refractory patients might respond to rituximab, a monoclonal antibody to the B-cell CD20 antigen.

**Neonates with transient maternally transmitted myasthenia gravis** require cholinesterase inhibitors for only a few days or occasionally for a few weeks, especially to allow feeding. No other treatment is usually necessary. In non–maternally transmitted congenital myasthenia gravis, identification of the specific molecular defect is important for treatment; Table 612-4 summarizes specific therapies for each type.

**Complications**

Children with myasthenia gravis do not tolerate neuromuscular-blocking drugs, such as succinylcholine and pancuronium, and may be paralyzed for weeks after a single dose. An anesthesiologist should carefully review myasthenic patients who require a surgical anesthetic and such anesthetics should be administered only by an experienced physician/anesthesiologist. Also, certain antibiotics can potentiate myasthenia and should be avoided; these include the aminoglycosides (gentamicin and others).

**Prognosis**

Some patients with autoimmune myasthenia gravis experience spontaneous remission after a period of months or years; others have a permanent disease extending into adult life. Immunosuppression, thymectomy, and treatment of associated hypothyroidism might provide a cure. Genetically determined congenital myasthenic syndromes may show initial worsening in infancy but then remain static throughout childhood and into adult life.

**Other Causes of Neuromuscular Blockade**

Organophosphate chemicals, commonly used as insecticides, can cause a myasthenia-like syndrome in children exposed to these toxins (see Chapter 63).

**Botulism** results from ingestion of food containing the toxin of *Clostridium botulinum*, a Gram-positive, spore-bearing, anaerobic bacillus (see Chapter 210). The mechanism is cleavage by the botulinum toxin of several of the structural glycoproteins of the wall (i.e., membrane) of synaptic vesicles within axonal terminals. These glycoproteins include synaptobrevin and synaptotagmin, but synaptophysin is resistant. Honey is a common source of contamination. The incubation period is short, only a few hours, and symptoms begin with nausea, vomiting, and diarrhea. Cranial nerve involvement soon follows, with diplopia, dysphagia, weak suck, facial weakness, and absent gag reflex. Generalized hypotonia and weakness then develop and can progress to respiratory failure. Neuromuscular blockade is documented by EMG with repetitive nerve stimulation. Respiratory support may be required for days or weeks until the toxin is cleared from the body. No specific antitoxin is available. Guanidine, 35 mg/kg/24 hr, may be effective for extraocular and limb muscle weakness but not for respiratory muscle involvement.

**Tick paralysis** is a disorder of ACh release from axonal terminals due to a neurotoxin that blocks depolarization. It also affects large
myelinated motor and sensory nerve fibers. This toxin is produced by the wood tick or dog tick, insects common in the Appalachian and Rocky Mountains of North America. The tick embeds its head into the skin, usually the scalp, and neurotoxin production is maximal about 5–6 days later. Motor symptoms include weakness, loss of coordination, and sometimes an ascending paralysis resembling Guillain-Barré syndrome. Tendon reflexes are lost. Sensory symptoms of tingling paresthesias can occur in the face and extremities. The diagnosis is confirmed by EMG and nerve conduction studies and by identifying the tick. The tick must be removed completely and the buried head not left beneath the skin. Patients then recover completely within hours or days.

Bibliography is available at Expert Consult.

### 612.2 Spinal Muscular Atrophies

**Harvey B. Sarnat**

Spinal muscular atrophies (SMAs) are degenerative diseases of motor neurons that begin in fetal life and continue to be progressive in infancy and childhood. The progressive denervation of muscle is compensated for in part by reinnervation from an adjacent motor unit, but giant motor units are thus created with subsequent atrophy of muscle fibers when the reinnervating motor neuron eventually becomes involved. Motor neurons of cranial nerves III, IV, and VI to extraocular muscles, as well as those of the sacral spinal cord innervating striated muscle of the urethral and anal sphincters, are selectively spared. Upper motor neurons (layer 5 pyramidal neurons in the cerebral cortex) also remain normal.

SMA is classified clinically into a severe infantile form, also known as **Werdnig-Hoffmann disease** or SMA type 1; a late infantile and more slowly progressive form, SMA type 2; and a more chronic or juvenile form, also called **Kugelberg-Welander disease**, or SMA type 3. A severe fetal form that is usually fatal in the perinatal period has been described as SMA type 0, with motor neuron degeneration demonstrated in the spinal cord as early as midgestation. These distinctions of types are based upon age at onset, severity of weakness, and clinical course; muscle biopsy does not distinguish types 1 and 2, though type 3 shows a more adult than perinatal pattern of denervation and reinnervation. Type 0 can show biopsy features more similar to myotubular myopathy because of maturational arrest; scattered myotubes and other immature fetal fibers also are demonstrated in the muscle biopsies of patients with types 1 and 2, but they do not predominate. Approximately 25% of patients have type 1, 50% type 2, and 25% type 3; type 0 is rare and accounts for <1%. Some patients are transitional between types 1 and 2 or between types 2 and 3 in terms of clinical function. A variant of SMA, **Fazio-Londe disease**, is a progressive bulbar palsy resulting from motor neuron degeneration more in the brainstem than the spinal cord, but cranial nerves of extraocular muscles also are spared in this form. Table 612-5 lists other variants.

Autonomic motor neurons of both the sympathetic and parasympathetic systems are not spared, but usually do not show clinical manifestations until late stages. Autonomic deficits may involve the detrusor muscle of the urinary bladder or the smooth muscle urethral and anal sphincters, in all 3 forms of SMA. In some patients with type 1 SMA and respiratory distress there may be severe autonomic dysregulation with dysautonomia and cardiovascular collapse leading to death or to severe ischemic brain damage.

### ETIOLOGY

The cause of SMA is genetic as an autosomal recessive mendelian trait. Neuropathologically it appears to be a pathologic continuation of a process of programmed cell death (apoptosis) that is normal in embryonic life. A surplus of motor neuroblasts and other neurons is generated from primitive neuroectoderm, but only about half survive and mature to become neurons; the excess cells have a limited life cycle and degenerate. If the process that arrests physiologic cell death fails to intervene by a certain stage, neuronal death can continue in late fetal life and postnatally. The survivor motor neuron gene (SMN) arrests apoptosis of motor neuroblasts. Unlike most genes that are highly conserved in evolution, SMN is a uniquely mammalian gene. An additional function of SMN, both centrally and peripherally, is to transport RNA-binding proteins to the axonal growth cone to ensure an adequate

<table>
<thead>
<tr>
<th>Table 612-4</th>
<th>Potential Therapies in Congenital Myasthenic Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AChE</strong></td>
<td>Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries</td>
</tr>
<tr>
<td></td>
<td>If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
</tr>
<tr>
<td></td>
<td>Avoid AChE inhibitors</td>
</tr>
<tr>
<td><strong>AChR deficiency</strong></td>
<td>AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses</td>
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<tr>
<td></td>
<td>If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
</tr>
<tr>
<td><strong>AChR fast channel</strong></td>
<td>AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses</td>
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<tr>
<td></td>
<td>If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
</tr>
<tr>
<td><strong>AChR slow channel</strong></td>
<td>Quinidine sulfate</td>
</tr>
<tr>
<td></td>
<td>Adults: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 µg/mL</td>
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<td></td>
<td>Children: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries</td>
</tr>
<tr>
<td></td>
<td>If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults</td>
</tr>
<tr>
<td></td>
<td>Avoid AChE inhibitors</td>
</tr>
<tr>
<td><strong>ChAT</strong></td>
<td>AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses</td>
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<tr>
<td></td>
<td>If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
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<tr>
<td><strong>Dok7</strong></td>
<td>Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries</td>
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<td></td>
<td>If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
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<td></td>
<td>Avoid AChE inhibitors</td>
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<tr>
<td><strong>Laminin β2</strong></td>
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<td></td>
<td>Avoid AChE inhibitors</td>
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<tr>
<td><strong>MuSK</strong></td>
<td>AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses</td>
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<td>3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
</tr>
<tr>
<td><strong>Rapsyn</strong></td>
<td>AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses</td>
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<tr>
<td></td>
<td>If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults</td>
</tr>
</tbody>
</table>

Bibliography


amount of protein-encoding transcripts essential for growth cone remodeling.

**CLINICAL MANIFESTATIONS**

The cardinal features of **SMA type 1** are severe hypotonia (Fig. 612-1); generalized weakness; thin muscle mass; absent tendon stretch reflexes; involvement of the tongue, face, and jaw muscles; and sparing of extraocular muscles and sphincters. Diaphragmatic involvement is late. Infants who are symptomatic at birth can have respiratory distress and are unable to feed. Congenital contractures, ranging from simple clubfoot to generalized arthrogryposis, occur in approximately 10% of severely involved neonates. Infants lie flaccid with little movement, unable to overcome gravity (see Fig. 607-1 in Chapter 607). They lack head control. More than 65% of children die by 2 yr of age, and many die early in infancy.

In **type 2 SMA**, affected infants are usually able to suck and swallow, and respiration is adequate in early infancy. These children show progressive weakness, but many survive into the school years or beyond, although confined to an electric wheelchair and severely handicapped. Nasal speech and problems with deglutition develop later. Scoliosis becomes a major complication in many patients with long survival. Gastroesophageal reflux may lead to malnutrition or to aspiration with acute airway obstruction or pneumonia.

**Kugelberg-Welander disease** is the mildest SMA (type 3), and patients can appear normal in infancy. The progressive weakness is proximal in distribution, particularly involving shoulder girdle muscles. Patients are ambulatory. Symptoms of bulbar muscle weakness are rare. Approximately 25% of patients with this form of SMA have muscular hypertrophy rather than atrophy, and it may easily be confused with a muscular dystrophy. Longevity can extend well into middle adult life. Fasciculations are a specific clinical sign of denervation of muscle. In thin children, they may be seen in the deltoid and biceps brachii muscles and occasionally the quadriceps femoris muscles, but the continuous, involuntary, worm-like movements may be masked by a thick pad of subcutaneous fat. Fasciculations are best observed in the tongue, where almost no subcutaneous connective tissue separates the muscular layer from the epithelium. If the intrinsic lingual muscles are contracted, such as in crying or when the tongue protrudes, fasciculations are more difficult to see than when the tongue is relaxed. Cramps and myalgias of appendicular and axial muscles are common, especially in later stages, and problems of micturition may present, though adolescent patients may be too embarrassed to state them unless the physician directly inquires.

The outstretched fingers of children with SMA often show a characteristic tremor owing to fasciculations and weakness. It should not be confused with a cerebellar tremor.

The heart is not involved in SMA. Intelligence is normal, and children often appear brighter than their normal peers because the effort they cannot put into physical activities is redirected to intellectual development, and they are often exposed to adult speech more than to juvenile language because of the social repercussions of the disease. Progressive deterioration of ambulation and the high risk of falling and fracturing long bones or the pelvis eventually require use of a
Part XXVIII  Neuromuscular Disorders

Muscle biopsy or chorionic villi tissues is available for diagnosis of

**GENETICS**

The extensive neuronal degeneration and gliosis in the ventral horns of loss or paresthesias. The most pronounced neuropathologic lesions are thalamus, but these alterations are not perceived clinically as sensory neurons of dorsal root ganglia and in somatosensory nuclei of the is seen. At autopsy, mild degenerative changes are seen in sensory neurons that span 20 kb and telomeric and centromeric exons that differ only by 5bp and produce a transcript encoding 294 amino acids. SMN1 is duplicated in a highly homologous gene called SMN2 and both genes are transcribed. SMN2 remains present in all patients with SMA, but cannot fully compensate the SMN1 defect. However, a molecular basis for correlation between the SMN2 copy number and clinical severity of the SMA is the capability of SMN2 to encode a small amount of an identical SMN protein. The critical difference between SMN1 and SMN2 genes is a cytosine (C) to thymine (T) transition in exon 7 of SMN2. Another gene, the neuronal apoptosis inhibitory gene (NAIP), is located next to the SMN gene and in many cases there is an inverted duplication with 2 copies, telomeric and centromeric, of both genes; isolated mutations or deletions of NAIP do not produce clinical SMA and generate a mostly nonfunctional isoform lacking the carboxy-terminal amino acids encoded by exon 7. Milder forms of SMA have more than 2 copies of SMN2, and in late-onset patients with homozygous deletion of the SMN1 gene, there are 4 copies of SMN2. An additional gene mapped to 11q13-q21 in SMA may help explain early respiratory failure in some patients. Nucleotide expansions account for only 5-10% of cases of SMA, and deletions or splicing out of exons 7 and 8 are the genetic mechanism in the great majority of cases. Another pair of genes adjacent to the SMN1 and SMN2 genes, SERF1 and SERF2, also may play a secondary role. The SMN gene product modulates axonal growth and localization of β-actin messenger RNA in growth cones of motor neurons. Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form also occurs. Carrier testing by dose analysis is available.

**LABORATORY FINDINGS**

The serum creatine kinase level may be normal but more commonly is mildly elevated in the hundreds. A creatine kinase level of several thousand is rare. The chest x-ray in early-onset disease demonstrates thin ribs. Results of motor nerve conduction studies are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy. EMG shows fibrillation potentials and other signs of denervation of muscle. A secondary mitochondrial DNA depletion is sometimes demonstrated in the muscle biopsy of infants with SMA. The molecular genetic test of the SMN gene provides definite confirmation of the diagnosis.

**DIAGNOSIS**

The simplest, most definitive diagnostic test is a molecular genetic marker in blood for the SMN gene. Muscle biopsy used to be the diagnostic test before the genetic marker from blood samples became available, and muscle biopsy now is used more selectively in patients showing equivocal or negative genetic findings. The muscle biopsy in infancy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle. Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers of both histochemical types (Fig. 612-2). Scattered immature myofibers resembling myotubes also are demonstrated. In juvenile SMA, the pattern may be more similar to adult muscle that has undergone many cycles of denervation and reinnervation. Neuromic changes in muscle also may be demonstrated by EMG, but the results are less definitive than by muscle biopsy in infancy. Sural nerve biopsy is now performed only occasionally, but shows mild sensory neuropathic changes, and sensory nerve conduction velocity may be slowed; hypertrophy of unmyelinated axons also is seen. At autopsy, mild degenerative changes are seen in sensory neurons of dorsal root ganglia and in somatosensory nuclei of the thalamus, but these alterations are not perceived clinically as sensory loss or paresthesias. The most pronounced neuropathologic lesions are the extensive neuronal degeneration and gliosis in the ventral horns of the spinal cord and brainstem motor nuclei, especially the hypoglossal nucleus.

**GENETICS**

Molecular genetic diagnosis by DNA probes in blood samples or in muscle biopsy or chorionic villi tissues is available for diagnosis of suspected cases and for prenatal diagnosis. Most cases are inherited as an autosomal recessive trait. The incidence of SMA is 10-15 in 100,000 live births, affecting all ethnic groups; it is the second most common neuromuscular disease, following Duchenne muscular dystrophy. The incidence of heterozygosity for autosomal recessive SMA is 1 in 50.

The genetic locus for all 3 of the common forms of SMA is on chromosome 5, a deletion at the 5q11-q13 locus, indicating that they are variants of the same disease rather than different diseases. The affected SMN1 gene has a molecular weight of 38 kDa and contains 8 exons that span 20 kb and telomeric and centromeric exons that differ only by 5bp and produce a transcript encoding 294 amino acids. SMN1 is duplicated in a highly homologous gene called SMN2 and both genes are transcribed. SMN2 remains present in all patients with SMA, but cannot fully compensate the SMN1 defect. However, a molecular basis for correlation between the SMN2 copy number and clinical severity of the SMA is the capability of SMN2 to encode a small amount of an identical SMN protein. The critical difference between SMN1 and SMN2 genes is a cytosine (C) to thymine (T) transition in exon 7 of SMN2. Another gene, the neuronal apoptosis inhibitory gene (NAIP), is located next to the SMN gene and in many cases there is an inverted duplication with 2 copies, telomeric and centromeric, of both genes; isolated mutations or deletions of NAIP do not produce clinical SMA and generate a mostly nonfunctional isoform lacking the carboxy-terminal amino acids encoded by exon 7. Milder forms of SMA have more than 2 copies of SMN2, and in late-onset patients with homozygous deletion of the SMN1 gene, there are 4 copies of SMN2. An additional gene mapped to 11q13-q21 in SMA may help explain early respiratory failure in some patients. Nucleotide expansions account for only 5-10% of cases of SMA, and deletions or splicing out of exons 7 and 8 are the genetic mechanism in the great majority of cases. Another pair of genes adjacent to the SMN1 and SMN2 genes, SERF1 and SERF2, also may play a secondary role. The SMN gene product modulates axonal growth and localization of β-actin messenger RNA in growth cones of motor neurons.

Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form also occurs. Carrier testing by dose analysis is available.

**TREATMENT**

No medical treatment is able to delay the progression. Supportive therapy includes orthopedic care with particular attention to scoliosis and joint contractures, mild physiotherapy, and mechanical aids for assisting the child to eat and to be as functionally independent as possible. Most children learn to use a computer keyboard with great skill but cannot use a pencil easily. Valproic acid is sometimes administered for control of seizures. Gene replacement and protein replacement therapies remain theoretical and experimental. Potential therapeutic genetic strategies in SMA include upregulation of SMN2 gene expression, preventing exon 7 skipping of SMN2 transcripts and improving the stability of the protein lacking the amino acid sequence encoded by exon 7.

Bibliography is available at Expert Consult.

**612.3 Other Motor Neuron Diseases**

Harvey B. Sarnat

Motor neuron diseases other than SMA are rare in children. Poliomyelitis used to be a major cause of chronic disability, but with the routine use of polio vaccine, this viral infection is now rare (see Chapter 249). Other enteroviruses, such as coxsackievirus and echovirus, or the live polio vaccine virus can also cause an acute infection of motor neurons with symptoms and signs similar to poliomyelitis, although usually
Bibliography
milder. Specific polymerase chain reaction tests and viral cultures of cerebrospinal fluid are diagnostic. Motor neuron infection with the West Nile virus also occurs.

A **juvenile form of amyotrophic lateral sclerosis** is rare. Upper and lower motor neuron loss is evident clinically, unlike in SMA. The course is progressive and ultimately fatal.

**Pena-Shokeir** and **Marden-Walker syndromes** are progressive motor neuron degenerations associated with severe arthrogryposis and congenital anomalies of many organ systems. **Pontocerebellar hypoplasias** are progressive degenerative diseases of the central nervous system that begin in fetal life; type 1 also involves motor neuron degeneration resembling an SMA, but the **SMN** gene on chromosome 5 is normal.

Motor neurons become involved in several metabolic diseases of the nervous system, such as gangliosidosis (Tay-Sachs disease), ceroid lipofuscinosis (Batten disease), and glycogenosis II (Pompe disease), but the signs of denervation may be minor or obscured by the more prominent involvement of other parts of the central nervous system or of muscle.
The hereditary motor-sensory neuropathies (HMSNs) are a group of progressive diseases of peripheral nerves (Table 613-1). Motor components generally dominate the clinical picture, but sensory and autonomic involvement is expressed later. Sural nerve biopsy used to be the most definitive means of diagnosis, but with the expanded knowledge

Text continued on p. 3003

<table>
<thead>
<tr>
<th>DISORDER (OMIM NO.)</th>
<th>CLINICAL FEATURES</th>
<th>NERVE CONDUCTION STUDIES</th>
<th>GENE OR LOCUS</th>
</tr>
</thead>
</table>
| **CMT1 (DEMYELINATING)**  
CMT1 A-F (HMSN type I) | Autosomal dominant. Onset 1st-4th decade. Predominant distal weakness, decreased DTRs, mild distal sensory loss, hypertrophy of nerves common | Delayed motor and sensory conduction studies. Motor studies typically <38 m/s | PMP22 duplication or point mutation |
| 1A (118220) | Commonest form recognized, seen in all ages (but more adults) | | MPZ |
| 1B (118200) | Approximately 5% of CMT1 group | | LITAF |
| 1C (601098) | Childhood onset, starts with abnormal gait, then distal weakness and wasting, occasional nerve hypertrophy. Rarely, early-onset hearing loss | | |
| 1D (607678) | Possible cranial nerve involvement. Late onset in childhood or early adulthood | | EGR2 |
| 1E (118300) | Associated with deafness (29-45%) | | |
| 1F (607734) | Hereditary neuropathy with liability to pressure palsies (tomaculous neuropathy) (162500) | | |
| Slowed NCVs | | | |
| Asymptomatic | | | |
| **CMT2 (AXONAL)**  
CMT2 A-L (HMSN type II) | Autosomal dominant. (A, B, D, E, F, G, I) Autosomal recessive (B, B2, H, K) Clinically similar to CMT type 1, except for later onset, absence of peripheral nerve enlargement, and less marked weakness | Nerve conduction velocities greater than HMSN type I (>38 m/s) but below normal range occasionally | 2A1: KIF1B (one family) 2A2: MFN2 2B: RAB7 2B1: LMNA 2B2: MED25 1q23–q24 2C: TRP4 1q23–q24 2D: GARS 2E: NEFL |
<p>| 2A1 (118210) | CMT2A: prominent distal weakness, proximal weakness also present in 60%. Optic atrophy and central involvement reported. Main form related to MFN2 mutations | | |
| 2A2 (609260) | | | |
| 2B (600882) | CMT2B: severe sensory loss: often complications with infections, arthropathy, amputations, foot ulcers, distal weakness | | |
| 2B1 (605588) | Average onset 34 yr (Costa Rican family) Vocal cord, diaphragm, and respiratory involvement, decreased longevity. Allelic with congenital dSMA (600175) and scapuloperoneal muscular atrophy (181405) | | |
| 2B2 (605589) | | | |
| 2C (606071) | | | |
| 2D (601472) (allelic to dSMA) | Upper limb predominance | | |
| 2E (607684) (1F dominant is allelic to CMT2E) | 30% associated with deafness, early childhood onset with gait abnormalities, occasional hyperkeratosis, increased sensory involvement | | |</p>
<table>
<thead>
<tr>
<th>DISORDER (OMIM NO.)</th>
<th>CLINICAL FEATURES</th>
<th>NERVE CONDUCTION STUDIES</th>
<th>GENE OR LOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2F (606595)</td>
<td>Trophic changes feet and knees</td>
<td>HSPB1 (HSP27)</td>
<td></td>
</tr>
<tr>
<td>2G (608591)</td>
<td>Onset age 9-76 yr, average age 20 yr, large Spanish family. Also severe form with early onset</td>
<td>12q12-q13</td>
<td></td>
</tr>
<tr>
<td>2H (607731)</td>
<td>Pyramidal involvement, vocal cord involvement</td>
<td>Intermediate/slow nerve conduction studies</td>
<td>GDAP1</td>
</tr>
<tr>
<td>2H (allelic to CMT4A–CMT4C2 in original publication)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2I (607677)</td>
<td>Onset age 9-76 yr, average age 20 yr, large Spanish family. Also severe form with early onset</td>
<td>12q12–q13</td>
<td></td>
</tr>
<tr>
<td>2J (607736)</td>
<td>Vocal cord paralysis, more severe early-onset form</td>
<td>MPZ</td>
<td></td>
</tr>
<tr>
<td>2K (607831)</td>
<td>Occasional proximal leg weakness (like dHMN II), large Chinese family, with onset at age 15-33 yr. Scoliosis</td>
<td>MPZ</td>
<td>GDAP1</td>
</tr>
<tr>
<td>2L (608673)</td>
<td>HSPB8</td>
<td>12q24</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>HMSN II with onset in early childhood (EOHMSN)</td>
<td>Autosomal dominant or recessive. Weakness within 1st 5 yr, rapid progression of weakness, usually complete paralysis below elbows and knees by 10 years. Absent DTRs, moderate sensory changes in most cases. Normal CSF protein. Occasional optic atrophy or spasticity</td>
<td>Axonal pattern with axonal-degenerative polyneuropathy. Absent SNAPs, no response to stimulation in cerebral palsy nerve, upper limb nerves normal or mildly slowed. EMG: denervation</td>
<td>MGASA</td>
</tr>
<tr>
<td>Severe early-onset axonal neuropathy (SEOAN)</td>
<td>Spinal muscular atrophy with respiratory distress type 1 (SMARD1)/severe infantile axonal neuropathy with respiratory failure (SINAR) Allelic to dHMN6 dSMA1 (604320)</td>
<td>Absent conduction in most cases</td>
<td>IGHMBP2</td>
</tr>
<tr>
<td>Hereditary motor and sensory neuropathy (HMSN-P) (Okinawa type)</td>
<td>Adult onset (after 30 yr). Autosomal dominant. Slowly progressive proximal dominant area of weakness. Fasciculations of extremities and trunk. Raised creatine kinase, hyperlipidemia, diabetes mellitus, eventual loss of ambulation, absent DTRs, sensory disturbances. Most patients described from Japan</td>
<td>Motor and sensory axonal neuropathy. SNAPs, CMAPs, MNCVs, and SNCVs reduced or absent EMG: fasciculations, fibrillations, and neuromyotonic picture early on</td>
<td>3q13</td>
</tr>
<tr>
<td>CMT3* AND 4</td>
<td>CMT3 (Dejerine-Sottas syndrome) (145900)</td>
<td>Motor conduction velocities usually &lt;10 m/s. SAPs absent. EMG: chronic denervation</td>
<td>PMP22, MPZ, PRX, EGR2, FIG4</td>
</tr>
<tr>
<td>CMT4 (A-J)</td>
<td>Autosomal recessive</td>
<td>Moderate slowing of nerve conduction studies</td>
<td>NDRG1</td>
</tr>
<tr>
<td>4A (214400)</td>
<td>Onset &lt;2 yr, Tunisian and Moroccan families. Severe progressive. Less-severe European phenotypes</td>
<td>25-35 m/s</td>
<td>GDAP1</td>
</tr>
<tr>
<td>4B1 (601382)</td>
<td>Ophthalmoplegia, vocal cord paralysis, facial, bulbar weakness (all infrequent). Weakness below 5 yr, proximal and distal weakness, absent DTRs</td>
<td>9-20 m/s</td>
<td>MTMR2 (MPZ)</td>
</tr>
<tr>
<td>4B2 (604563)</td>
<td>Early onset: 1st decade; glaucoma and deafness sometimes. Recorded in Tunisia, Japan, and Turkey</td>
<td>15-30 m/s</td>
<td>SBF2, MTMR13</td>
</tr>
<tr>
<td>4C (601596)</td>
<td>Early-onset scoliosis, commoner in Algerians, glaucoma and neutropenia. 1st and 2nd decades</td>
<td>4-37 m/s</td>
<td>SH3TC2 (KIAA1985)</td>
</tr>
<tr>
<td>4D (601455) (HMSN-Lom)</td>
<td>Closed gypsy pedigree; onset &lt;10 yr. Deafness (by 2nd-3rd decade). Tongue atrophy</td>
<td>10-20 m/s</td>
<td>NDRG1</td>
</tr>
<tr>
<td>4E (605253)</td>
<td>Congenital hypomyelinating neuropathy</td>
<td>5-20 m/s</td>
<td>ERG2/KROX 20, MPZ</td>
</tr>
</tbody>
</table>
### Table 613-1 Hereditary Peripheral Neuropathies—cont’d

<table>
<thead>
<tr>
<th>DISORDER (OMIM NO.)</th>
<th>CLINICAL FEATURES</th>
<th>NERVE CONDUCTION STUDIES</th>
<th>GENE OR LOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F (145900)</td>
<td>Severely affected at birth or by 7 y; arthrogryposis multiplex congenita common; respiratory and feeding difficulties; often die young</td>
<td>&lt;5 m/s</td>
<td>PRX</td>
</tr>
<tr>
<td>4G (605285)</td>
<td>Type Russe. Onset 8-16 yr. Origin Bulgaria</td>
<td>30-35 m/s</td>
<td>10q22</td>
</tr>
<tr>
<td>4H (609311)</td>
<td>Increased in Lebanese/Turkish. Onset to childhood (1-2 yr). Delayed motor milestones. Occasional scoliosis, increased distal weakness, usually absent DTRs</td>
<td>&lt;10 m/s or absent</td>
<td>FDG4</td>
</tr>
<tr>
<td>4J (611228)</td>
<td>Onset by 5 yr. Severe disorder. Similarities to motor neuron disease</td>
<td>2-7 m/s; some cases higher</td>
<td>FIG4</td>
</tr>
<tr>
<td>CCFDN (604168)</td>
<td>Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy</td>
<td>19-33 m/s</td>
<td>CTDP1</td>
</tr>
</tbody>
</table>

**MIXED PATHOLOGY (AXONAL AND Demyelinating)**

- **CMT X**
  - Median nerve motor conduction studies <40 m/s (but faster than CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced.
  - GJB1

- **X2 (302801)**: X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected.
  - Mixed demyelinating/axonal
  - Xq22.2

- **X3 (302802)**: X-linked recessive. ± Spasticity. Females unaffected.
  - Mixed demyelinating/axonal
  - Xq26

  - Xq24–26.1

- **X5 (311070)**: X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes.
  - Axonal neuropathy–mild demyelinating changes
  - Xq21.32–q24

**Intermediate forms of CMT**

- Patients have neurophysiologic results that fall between axonal and demyelinating ranges
  - “Intermediate values” 30-40 m/s—most accurate from median motor nerves. Some forms have normal nerve conduction studies (DI-CMTB).

**DI-CMTA**

- Italian family

**DI-CMTB (606482)**

- American family

**DI-CMTD (607791)**

- Myelin protein zero

**DI-autoosomal recessive form (608340)**

- Overlap conditions: Recessive CMT with GADP1 mutations: (CMT2K and 4A) Spanish and Tunisian family–severe childhood forms reported. Also called DI-CMTA autosomal recessive form CMT with NF-L: (CMT1F and 2E).

**DI-CMTA**

- Small/absent SNAPs. Motor studies axonal in type

**DI-CMTB (606482)**

- 10q24.1–q25.1

**DI-CMTD (608323)**

- DNMT2

**DI-CMTD (607791)**

- MPZ

**DI-autoosomal recessive form (608340)**

- GJB1

**DI-CMTA**

- NF-L

**DI-CMTB (606482)**

- GDAP1

**DI-CMTD (608323)**

- YARS

**DI-autoosomal recessive form (608340)**

- Myelin protein zero

**DI-CMTA**

- Small/absent SNAPs. Motor studies axonal in type

**DI-CMTB (606482)**

- SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1

**DI-CMTD (608323)**

- CMT with pyramidal signs: MFN2

**DI-autoosomal recessive form (608340)**

- CMT with pyramidal signs: MFN2

**OTHER HMSN AND HMN SYNDROMES**

**HMSN V/spastic paraplegia with HMSN type V/CMT5 (CMT with pyramidal signs) (600631)**

- Variable inheritance. Spasticity in lower limbs causing difficulty walking and toe walking. Autosomal recessive form associated with mental retardation. Lower limb marked spasticity with little weakness, increased DTRs, extensor plantars, pes cavus, often distal amyotrophy. Expanding field with multiple subforms, n = 37. Not all associated with peripheral neuropathy.

**HMSN VI (allelic CMT2A)**

- CMT with pyramidal signs: part of HMSN V but described without spasticity.

**HMSN VII**


**HMSN VI (allelic CMT2A)**

- No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated

**HMSN VII**

- HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset.

Continued
### Table 613-1  Hereditary Peripheral Neuropathies—cont’d

<table>
<thead>
<tr>
<th>DISORDER (OMIM NO.)</th>
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<th>GENE OR LOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISTAL HEREDITARY MOTOR NEUROPATHIES (dHMN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dHMN (182960)</td>
<td>Autosomal dominant. Juvenile onset. Distal weakness and wasting</td>
<td>Normal nerve conduction studies, occasional mild slowing. EMG neurogenic</td>
<td>Hspb1, 7q34–q36</td>
</tr>
<tr>
<td>dHMN (608634)</td>
<td>Autosomal dominant. Adult onset, distal weakness and wasting</td>
<td></td>
<td>Hspb8, Hspb3</td>
</tr>
<tr>
<td>dHMNII (158590)</td>
<td>(Allelic CMT2F, CMT2L)</td>
<td></td>
<td>Hspb1</td>
</tr>
<tr>
<td>dHMNIIjuv (158590)</td>
<td>Autosomal recessive. Infantile to adult onset. Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis</td>
<td></td>
<td>11q13.3</td>
</tr>
<tr>
<td>dHMNIV (607088)</td>
<td>Autosomal recessive. Juvenile onset. Severe muscle wasting and weakness and diaphragmatic paralysis</td>
<td></td>
<td>11q13</td>
</tr>
<tr>
<td>Distal SMA type 3</td>
<td>(Allelic CMT2D)</td>
<td></td>
<td>Gars</td>
</tr>
<tr>
<td>dHMNV (600794)</td>
<td>Autosomal dominant. Upper limb predominance, occasional pyramidal features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dHMN type V (Silver syndrome) (270685)</td>
<td>Autosomal dominant. Prominent hand muscle weakness and wasting, mild to severe spasticity of lower limbs</td>
<td></td>
<td>BSCL2</td>
</tr>
<tr>
<td>dHMNV (604320)</td>
<td>Autosomal recessive. Severe infantile form with respiratory distress</td>
<td></td>
<td>Ighmbp2</td>
</tr>
<tr>
<td>dHMNVI (158580)</td>
<td>Autosomal dominant. Onset with vocal cord paralysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked dHMN (602433)</td>
<td>X-linked recessive. Juvenile onset with distal wasting and weakness</td>
<td></td>
<td>SETX</td>
</tr>
<tr>
<td>dHMN-J (Jeras)</td>
<td>Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs</td>
<td></td>
<td>9p21.1–p12</td>
</tr>
<tr>
<td>Congenital distal SMA (600175)</td>
<td>Autosomal recessive. Onset from 6-10 yr with pyramidal features in 1 Jordanian family</td>
<td>Autosomal dominant congenital nonprogressive distal HMN with contractures</td>
<td>12q23–q24</td>
</tr>
<tr>
<td>Hereditary neuralgic amyotrophy (brachial plexus neuropathy) (162100)</td>
<td>Autosomal dominant. Episodes of paralysis and muscle weakness initiated by severe pain. Onset can be from birth or later childhood but usually adult onset. Outcome usually good but some left with residual dysfunction. Episodes often triggered by infections, immunizations, and stress. Some pedigrees dysmorphic with hypotelorism</td>
<td>Normal or mildly prolonged MNCVs distal to affected brachial plexus</td>
<td>SEPT9</td>
</tr>
</tbody>
</table>

### HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

| HSN (HSAN) 1 (162400)                      | Type 1: Autosomal dominant. Onset 2nd–5th decade. Predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement | Normal to low-normal MNCVs, disturbance of sensory conduction of variable severity | Sptlc1, RAB7, 3p24–p22 |
| HSN (HSAN) 2(A) (201300)                  | Autosomal recessive. Onset in infancy/early childhood–1st 2 decades. Mutilating acropathy. Often unrecognized fractures. Marked sensory loss affecting all cutaneous modalities, most marked distally in all limbs. Autonomic dysfunction less marked. Absent or decreased DTRs | Normal MNCVs; SNAPs are absent | Wnk1          |
| HSN (HSAN) 2B (223900)                    | Autosomal recessive. Impaired sensation, ulcers, and arthropathy develop in childhood |                                                       | Fam1348       |
of the molecular genetics of this group of diseases, the diagnosis of most can be confirmed by less invasive genetic testing. Electromyography (EMG) remains a useful adjunct to clinical diagnosis and helps distinguish between demyelinating or hypomyelinating and axonal forms.

Classification of HMSN is difficult because no single unifying scheme is capable of incorporating all the clinical presentations and overlapping genetics (see Table 613-1). In some neuropathies, a diverse genotype of mutations of different genes at different chromosomal loci may produce a similar phenotype. One classification identifies: I. Hereditary neuropathies secondary to general diseases; II. Primary hereditary neuropathy; III. Hereditary motor neuronopathy; IV. Hereditary sensory and autonomic neuropathy; V. Hereditary sensory neuropathy; MNCV, motor nerve conduction velocity; OMIM, Online Mendelian Inheritance in Man; SAP, sensory action potential; SEOAN, severe early-onset axonal neuropathy; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential.


**613.1 Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease, Hereditary Motor-Sensory Neuropathy Type IIa)**

Harvey B. Sarnat

Charcot-Marie-Tooth disease is the most common genetically determined neuropathy and has an overall prevalence of 3.8/100,000 population. It is transmitted as an autosomal dominant trait with 83% expressivity; the 17p11.2 locus is the site of the abnormal gene. Autosomal recessive transmission also is described but is rarer. The gene product is peripheral myelin protein 22 (PMP22). A much rarer X-linked HMSN type I results from a defect at the Xq13.1 locus, causing mutations in the gap junction protein connexin-32. Other forms have been reported (see Table 613-1).

**CLINICAL MANIFESTATIONS**

Most patients are asymptomatic until late childhood or early adolescence, but young children sometimes manifest gait disturbance as early as the 2nd yr of life. The peroneal and tibial nerves are the earliest and most severely affected. Children with the disorder are often described as being clumsy, falling easily, or tripping over their own feet. Application of the Cumberland Ankle Instability Tool for Youth is a means of objectively documenting and following this manifestation. The onset of symptoms may be delayed until after the 5th decade.

Muscles of the anterior compartment of the lower legs become wasted, and the legs have a characteristic stork-like contour. The muscular atrophy is accompanied by progressive weakness of dorsiflexion of the ankle and eventual footdrop. The process is bilateral but may be slightly asymmetric. Pes cavus deformities invariably develop as a result of denervation of intrinsic foot muscles, further destabilizing the gait. Atrophy of muscles of the forearms and hands is usually not as severe as that of the lower extremities, but in advanced cases contractures of the wrists and fingers produce a claw hand. Proximal muscle weakness is a late manifestation and is usually mild. Axial muscles are not involved.

The disease is slowly progressive throughout life, but patients occasionally show accelerated deterioration of function over a few years. Most patients remain ambulatory and have normal longevity, although orthotic appliances are required to stabilize the ankles.

Sensory involvement mainly affects large myelinated nerve fibers that convey proprioceptive information and vibratory sense, but the threshold for pain and temperature can also increase. Some children complain of tingling or burning sensations of the feet, but pain is rare. Because the muscle mass is reduced, the nerves are more vulnerable to trauma or compression. Autonomic manifestations may be expressed as poor vasomotor control with blotching or pallor of the skin of the feet and inappropriately cold feet.
Nerves often become palpably enlarged. Tendon stretch reflexes are lost distally. Cranial nerves are not affected. Sphincter control remains well preserved. Autonomic neuropathy does not affect the heart, gastrointestinal tract, or bladder. Intelligence is normal. A unique point mutation in PMP22 causes progressive auditory nerve deafness in addition, but this is usually later in onset than the peripheral neuropathy. 

Davidenkow syndrome is a variant of HMSN type I with a scapuloperoneal distribution.

**LABORATORY FINDINGS AND DIAGNOSIS**

Motor and sensory nerve conduction velocities are greatly reduced, sometimes as slow as 20% of normal conduction time. In new cases without a family history, both parents should be examined, and nerve conduction studies should be performed.

EMG and muscle biopsy are not usually required for diagnosis, but they show evidence of many cycles of denervation and reinnervation. Serum creatine kinase level is normal. Cerebrospinal fluid (CSF) protein may be elevated, but no cells appear in the CSF.

Sural nerve biopsy is diagnostic. Large- and medium-size myelinated fibers are reduced in number, collagen is increased, and characteristic onion bulb formations of proliferated Schwann cell cytoplasm surround axons. This pathologic finding is called interstitial hypertrophic neuropathy. Extensive segmental demyelination and remyelination also occur.

The definitive molecular genetic diagnosis may be made in blood.

**TREATMENT**

Stabilization of the ankles is a primary concern. In early stages, stiff boots that extend to the mid calf often suffice, particularly when patients walk on uneven surfaces such as ice and snow or stones. As the dorsiflexors of the ankles weaken further, lightweight plastic splints may be custom made to extend beneath the foot and around the back of the ankle. They are worn inside the socks and are not visible, reducing self-consciousness. External short-leg braces may be required when footdrop becomes complete. Surgical fusion of the ankle may be considered in some cases.

The leg should be protected from traumatic injury. In advanced cases, compression neuropathy during sleep may be prevented by placing soft pillows beneath or between the lower legs. Burning paresthesias of the feet are not common but are often abolished by phenytoin, carbamazepine, or gabapentin. No medical treatment is available to arrest or slow the progression.

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**613.2 Peroneal Muscular Atrophy (Axonal Type)**

Harvey B. Sarnat

Peroneal muscular atrophy is clinically similar to HMSN type I, but the rate of progression is slower and the disability is less. EMG shows denervation of muscle. Sural nerve biopsy reveals axonal degeneration rather than the demyelination and whorls of Schwann cell processes typical in type I. The locus is on chromosome 1 at 1p35-p36; this is a different disease than HMSN type I, although both diseases are transmitted as autosomal dominant traits. An autosomal recessive infantile motor axonal neuropathy can closely mimic infantile spinal muscular atrophy.

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**613.3 Congenital Hypomyelinating Neuropathy and Dejerine-Sottas Disease (Hereditary Motor-Sensory Neuropathy Type III)**

Harvey B. Sarnat

Congenital hypomyelinating neuropathy is an interstitial hypertrophic neuropathy of autosomal dominant transmission, clinically similar to HMSN type I but more severe. Symptoms develop in early infancy and are rapidly progressive, with hypotonia and breathing and feeding difficulties. Pupillary abnormalities, such as lack of reaction to light and Argyll Robertson pupil, are common. Kyphoscoliosis and pes cavus deformities complicate approximately 35% of cases. Nerves become palpably enlarged at an early age. Dejerine-Sottas disease is a more slowly progressive variant with onset usually before age 5 yr.

An autosomal recessive form of congenital hypomyelinating neuropathy also is known and may be caused by various genetic mutations, including MTMR2, PMP22, EGR2, and MPZ. Neonatal hypotonia and developmental delay in infancy are hallmark clinical features. Many patients exhibit congenital insensitivity to pain. Cranial nerves are inconsistently involved, and respiratory distress and dysphagia are rare complications. Tendon reflexes are absent. Arthrogryposis is present at birth in at least half the cases.

The onion bulb formations seen in the sural nerve biopsy specimen are pronounced. Hypomyelination also occurs. In the recessive form, hypomyelination may not be accompanied by interstitial hypertrophy in all cases.

The genetic locus of 17p11.2 is identical to that of HMSN type I or Charcot-Marie-Tooth disease. Monoallelic mutations in MPZ (myelin protein zero), PMP22, or EGR2 (early grow response 2) are the most frequent genetic causes. The clinical and pathologic differences may be phenotypical variants of the same disease, analogous to the situation in Duchenne and Becker muscular dystrophies. An autosomal recessive form of Dejerine-Sottas disease is incompletely documented.

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**613.4 Roussy-Lévy Syndrome**

Harvey B. Sarnat

Roussy-Lévy syndrome is defined as a combination of HMSN type II and cerebellar deficit resembling Friedreich ataxia, but it does not have cardiomyopathy.

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**613.5 Refsum Disease (Hereditary Sensory Neuropathy Type IV) and Infantile Refsum Disease**

Harvey B. Sarnat

See Chapter 86.2.

Refsum disease is a rare autosomal recessive disease caused by an enzymatic block in β-oxidation of phytanic acid to pristanic acid. Phytanic acid is a branched-chain fatty acid that is derived mainly from dietary sources: spinach, nuts, and coffee. Levels of phytanic acid are greatly elevated in plasma, CSF, and brain tissue. The CSF shows an albuminocytologic dissociation, with a protein concentration of 100-600 mg/dL. Genetic linkage studies identify 2 distinct loci at 10q24 and 10q26 genes, which produce both clinical and biochemical differences from the classical form, and include minor facial dysmorphism, retinitis pigmentosa, sensorineurual hearing loss, hypercholesterolemia, hepatomegaly, and failure to thrive. Phytanic acid accumulation in infantile Refsum disease is secondary to a primary peroxisomal disorder; hence autosomal recessive Refsum disease is really a different disease.

Clinical onset of classical Refsum disease is usually between 4 and 7 yr of age, with intermittent motor and sensory neuropathy. Ataxia, progressive neurosensory hearing loss, retinitis pigmentosa with loss of night vision, ichthyosis, and liver dysfunction also develop in various degrees. Skeletal malformations from birth and cardiac findings of conduction disturbances and cardiomyopathy appear in the majority. Motor and sensory nerve conduction velocities are delayed. Sural nerve biopsy shows loss of myelinated axons. Treatment is by dietary management and periodic plasma exchange. With careful management, life expectancy can be normal.
613.6  Fabry Disease
Harvey B. Samnat

See Chapter 86.4.

Fabry disease, a rare X-linked recessive trait, results in storage of ceramide trihexose because of deficiency of the enzyme ceramide trihexosidase, which cleaves the terminal galactose from ceramide trihexose (ceramide-glucose-galactose-galactose), resulting in tissue accumulation of this trihexose lipid in central nervous system neurons, Schwann cells and perineurial cells, ganglion cells of the myenteric plexus, skin, kidneys, blood vessel endothelial and smooth muscle cells, heart, sweat glands, cornea, and bone marrow. It results from a missense mutation disrupting the crystallographic structure of α-galactosidase A.

CLINICAL MANIFESTATIONS
The presentation is in late childhood or adolescence, with recurrent episodes of burning pain and paresthesias of the feet and lower legs so severe that patients are unable to walk. These episodes are often precipitated by fever or by physical activity. Objective sensory and motor deficits are not demonstrated on neurologic examination, and reflexes are preserved. Characteristic skin lesions are seen in the perineal region, scrotum, buttocks, and periumbilical zone as flat or raised red-black telangiectases known as angiookeratoma corporis diffusum. Hypohidrosis may be present. Corneal opacities, cataracts, and necrosis of the femoral heads are inconstant features. Tortuosity of retinal vessels and of the vertebral and basilar arteries can occur. The disease is progressive. Hypertension and renal failure are usually delayed until early adult life. Recurrent strokes result from vascular wall involvement. Death often occurs in the 5th decade owing to cerebral infarction or renal insufficiency, but a significant morbidity already occurs in childhood despite the absence of major organ failure. Heterozygous female carriers may be asymptomatic or, rarely, are as affected as males; corneal opacities involve 70-80%, though cataracts are rare.

LABORATORY FINDINGS
Motor and sensory nerve conduction velocities are normal to only mildly slow, showing preservation of large myelinated nerve fibers. CSF protein is normal. Proteinuria is present early in the course.

Calcifications often are seen in pulvinar of the thalamus, as demonstrated by CT or MRI and are specific imaging findings, believed caused by cerebral hyperperfusion. Positron tomography, by contrast, shows reduced cerebral blood flow velocity and impaired autoregulation because of the glycosphingolipid storage in vascular endothelial cells.

Pathologic features are usually first detected in skin or sural nerve biopsy specimens. Electron microscopy demonstrates crystalline glycosphingolipids, appearing as zebra bodies, in lysosomes of endothelial cells, in smooth myocytes of arterioles, and in Schwann cells. Nerves show a selective loss of small myelinated fibers and relative preservation of large and medium-sized axons, contrasting to most axonal neuropathies in which large myelinated fibers are most involved.

Assay for the deficient enzyme, α-galactosidase-A, may be performed from skin fibroblasts, leukocytes, and other tissues. This test permits detection of the female carrier state and provides a reliable means of prenatal diagnosis.

TREATMENT
See Chapter 86.4 for specific therapy of Fabry disease, including enzyme replacement.

Medical therapy of painful neuropathies includes management of the initiating disease and therapy directed to the neuropathic pain independent of etiology. Pain may be burning or associated with paresthesia, hyperalgesia (abnormal response to noxious stimuli), or allodynia (induced by non–noxious stimuli; see Chapter 62). Neuropathic pain is often successfully managed by tricyclic antidepressants; selective serotonin reuptake inhibitors are less effective. Anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine) are effective, as are narcotic and nonnarcotic analgesics. Enzyme replacement therapy has improved the short- and long-term prognosis of the clinical neuropathy and also reverses the increased blood flow velocity in the brain.

613.7  Giant Axonal Neuropathy
Harvey B. Samnat

Giant axonal neuropathy is a rare autosomal recessive disease with onset in early childhood. It is a progressive mixed peripheral neuropathy and degeneration of central white matter, similar to the leukodystrophies. Ataxia and nystagmus are accompanied by signs of progressive peripheral neuropathy. A large majority of affected children have frizzy hair, which microscopically shows variation in diameter of the shaft and twisting, similar to that in Menkes disease; hence, microscopic examination of a few scalp hairs provides a simple screening tool in suspected cases. Focal axonal enlargements are seen in both the peripheral nervous system and the central nervous system, but the myelin sheath is intact. The disease is a general proliferation of intermediate filaments, including neurofilaments in axons, glial filaments (i.e., Rosenthal fibers) in brain, cytotkeratin in hair, and vimentin in Schwann cells and fibroblasts.

Nonsense and missense mutations or deletions occur in the GAN gene, with allelic heterogeneity, at 16q24. These mutations are responsible for defective synthesis of the protein gigaxonin, a member of the cytoskeletal BTB/kelch superfamily, crucial to linkage between intermediate proteins and the cell membrane. MRI shows white matter lesions of the brain similar to leukodystrophies, and MR spectroscopy demonstrates increased ratios of choline:creatinine and myoinositol:creatinine, with a normally preserved ratio of N-acetyl aspartate: creatine, indicating demyelination and glial proliferation without axonal loss. Gigaxonin is expressed in a wide variety of neuronal cell types and is localized to the Golgi apparatus and endoplasmic reticulum.

The diagnosis is established by microscopy of scalp hair and by MRI and MR spectroscopy of the brain; it is confirmed by sural nerve biopsy and/or by genetic studies, if available, of the GAN gene. A mutation of BAG3, one of several genes associated with myofibrillar myopathy (see Chapter 608.5), also can cause giant axonal neuropathy as another genetic etiology not associated with the more frequent GAN gene.

613.8  Tomaculous (Hypermyelinating) Neuropathy; Hereditary Neuropathy with Liability to Pressure Palsies
Harvey B. Samnat

This hereditary neuropathy is characterized by redundant overproduction of myelin around each axon in an irregular segmental fashion so that tomaculous (sausage-shaped) bulges occur in the individual myelinated nerve fibers. Other sections of the same nerve can show loss of myelin. Such nerves are particularly prone to pressure palsies, and patients, usually beginning in adolescence, present with recurrent or intermittent mononeuropathies secondary to minor trauma or entrapment neuropathies, such as carpal tunnel syndrome, peroneal palsies, and even “writer’s cramp.” It is transmitted as an autosomal dominant trait, with loci identified at 17p11.2 and 17p12, deletion of exons in the PMP22 gene, in some patients only microdeletions. Duplication of the same 17p12 locus leads to Charcot-Marie-Tooth disease type 1A, myelin protein zero (MPZ) gene mutation. Sural nerve biopsy is diagnostic, but special teased fiber preparations should be made to demonstrate the myelin abnormalities most clearly. Skin or conjunctival biopsies also may be diagnostic. Electrophysiologic nerve conduction studies are abnormal but nonspecific. Genetic studies are definitive.

Treatment is supportive and includes avoiding trauma and prolonged nerve compression, including postures when sitting or lying.
Surgical release of entrapped nerves is indicated at times, particularly of the ulnar nerve.

613.9 **Leukodystrophies**

*Harvey B. Sarnat*

Several hereditary degenerative diseases of white matter of the central nervous system also cause peripheral neuropathy. The most important are Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, and adrenoleukodystrophy (see Chapters 86 and 599).

*Bibliography is available at Expert Consult.*
Bibliography


Many chemicals (organophosphates), toxins, and drugs can cause peripheral neuropathy (Table 614-1). Heavy metals are well-known neurotoxins. Lead poisoning, especially if chronic, causes mainly a motor neuropathy selectively involving large nerves, such as the common peroneal, radial, and median nerves, a condition known as mononeuritis multiplex (see Chapter 721). Arsenic produces painful burning paresthesias and motor polyneuropathy. Exposure to industrial and agricultural chemicals is a less-common cause of toxic neuropathy in children than in adults, but insecticides are neurotoxins for both insects and humans, and if they are used as sprays in closed spaces, they may be inhaled and induce lethargy, vomiting, seizures, and neuropathy, particularly with recurrent or long-term exposure. Working adolescents and children in developing countries are at risk. Puffer fish poisoning, which can be acquired even when fish contaminated with the venom has been cooked, produces a Guillain-Barré–like syndrome. Ethanol abuse can be neurotoxic and particularly affects the optic nerves, but optic neuritis is not a true peripheral neuropathy.

The most frequent cause of toxic neuropathies in children is prescribed medications, though street drugs also can be neurotoxic. Anti-metabolic and immunosuppressive drugs, such as vincristine, cisplatin, and paclitaxel, produce polyneuropathies as complications of chemotherapy for neoplasms and immunologic disorders, such as juvenile idiopathic arthritis. This "iatrogenic" cause is usually an axonal degeneration rather than primary demyelination, unlike primary autoimmune neuropathies. Excessive vitamin intake ("megavitamins") can be neurotoxic.

Chronic uremia is associated with toxic neuropathy and myopathy. The neuropathy is caused by excessive levels of circulating parathyroid hormone. Reduction in serum parathyroid hormone levels is accompanied by clinical improvement and a return to normal of nerve conduction velocity. Peripheral nerve axonal damage, particularly of small fibers, can be secondary to mitochondrial loss or dysfunction in toxic neuropathies. Abnormal toxic complex lipids, generated in Schwann cells by deficient mitochondrial respiration, are capable of damaging or destroying neighboring axons, a secondary mitochondrial toxic neuropathy. Small heat-shock proteins can be provoked that also may contribute to toxic neuropathy.

Biologic neurotoxins associated with diphtheria, Lyme disease, West Nile virus disease, leprosy, herpesviruses (Bell palsy), and rabies also produce peripheral nerve– or ventral horn cell–induced weakness or paralysis. HIV infections also produce neuropathy and this infection is particularly prevalent in children in several African countries, including those who immigrate to western countries as refugees. Tick paralysis, botulism, and paralytic shellfish poisoning cause neuromuscular junction blockade rather than true neuropathy. Various inborn errors of metabolism are also associated with peripheral neuropathy from metabolite toxicity or deficiencies (see Part XI and Table 614-1).

Bibliography is available at Expert Consult.

<table>
<thead>
<tr>
<th>Table 614-1</th>
<th>Toxic and Metabolic Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METALS</strong></td>
<td>Nitrofurantoin</td>
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<tr>
<td>Arsenic (insecticide, herbicide)</td>
<td>Nitrous oxide</td>
</tr>
<tr>
<td>Lead (paint, batteries, pottery)</td>
<td>Nucleosides (antiretroviral agents dideoxycytidine [ddC], didanosine [ddl], d4T, others)</td>
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<tr>
<td>Mercury (metallic, vapor)</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Thallium (rodenticides)</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Gold</td>
<td>Phenytoin</td>
</tr>
<tr>
<td><strong>OCCUPATIONAL OR INDUSTRIAL CHEMICALS</strong></td>
<td>Pyridoxine (excessive)</td>
</tr>
<tr>
<td>Acrylamide (grouting, flocculation)</td>
<td>Statins</td>
</tr>
<tr>
<td>Carbon disulfide (solvent)</td>
<td>Stibamidine</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Suramin</td>
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<tr>
<td>Dichlorophenoxyacetate</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Dimethylaminopropionitrile</td>
<td>Taxanes (paclitaxel, docetaxel)</td>
</tr>
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<td>Ethylene oxide (gas sterilization)</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Hexacarbons (glue, solvents)</td>
<td>Tryptophan (eosinophilia–myalgia syndrome)</td>
</tr>
<tr>
<td>Organophosphates (insecticides, petroleum additive)</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td><strong>METABOLIC DISORDERS</strong></td>
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<tr>
<td>Tetrachlorobiphenyl</td>
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<td>Trichloroethylene</td>
<td>Krabbe disease</td>
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<td><strong>DRUGS</strong></td>
<td>Leukodystrophies</td>
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<td>Amiodarone</td>
<td>Porphyria</td>
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<td>Chloramphenicol</td>
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<td>Tyrosinemia</td>
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<td>Cisplatin</td>
<td>Uremia</td>
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<td>Colchicine</td>
<td><strong>BIOLOGIC AND INFECTIOUS NEUROPATHIES</strong></td>
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<td>Diphtheria</td>
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<td>Ethambutol</td>
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<td>Fluoroquinolones</td>
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<td>Isoniazid</td>
<td><strong>West Nile virus</strong></td>
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<td>Metronidazole</td>
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Bibliography
Involvement of small, lightly or unmyelinated autonomic nerve fibers may be seen in many peripheral neuropathies; the autonomic manifestations are usually mild or subclinical. Certain autonomic neuropathies are more symptomatic and demonstrate varying degrees of involvement of the autonomic nervous system regulation of the cardiovascular, gastrointestinal, genitourinary, thermoregulatory, sudomotor, and pupillomotor systems. Figure 615-1 shows the classification of autonomic disorders (dysautonomias).

The differential diagnosis is noted in Tables 613-1 (in Chapter 613) and 615-1; Table 615-2 compares the neonatal-infantile onset
Classification of autonomic disorders or dysautonomias. The first conceptual division is between a structural and functional disorder. The word “functional” is being used in its true meaning of a disturbance in autonomic function, without clear evidence of structural damage to the autonomic nervous system, akin to the use of the word “functional” in functional gastrointestinal disorders, and without implication of a psychiatric etiology. In the absence of any evidence of consistent structural abnormalities functional disorders clearly cannot be localized in the nervous system. In contrast, structural disorders can be further divided into those localized in the central and peripheral nervous systems, with the division point usually taken at the sympathetic ganglion. Finally, peripheral nervous system disorders can be further classified based on whether they primarily involve afferent or efferent nerves. It should be emphasized that there is overlap between these groups, for example, diabetes will often involve afferent nerve fibers, but this classification emphasizes the predominant fiber involvement. A dotted line links Parkinson disease to a peripheral efferent group as Lewy bodies are present in both parasympathetic and sympathetic ganglia, impairing peripheral autonomic function. See below for discussion of specific disorders. CCHS, Congenital central hypoventilation syndrome; HSAN, hereditary sensory autonomic neuropathy. (From Chelimsky T, Robertson D, Chelimsky G: Disorders of the autonomic nervous system. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors: Bradley’s neurology in clinical practice, ed 6, Philadelphia, 2012, WB Saunders, Fig. 77-1, p. 2018.)

### Table 615-1  Autonomic Neuropathies

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tr>
<td>Guillain-Barré syndrome (see Chapter 608)</td>
<td>Non–Guillain-Barré syndrome autoimmunity</td>
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<tr>
<td></td>
<td>Paraneoplastic (type I antineuronal nuclear antibody)</td>
</tr>
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<td></td>
<td>Lambert-Eaton syndrome</td>
</tr>
<tr>
<td></td>
<td>Antibodies to neuronal nicotinic acetylcholine receptors</td>
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<td></td>
<td>Antibodies to P/Q-type calcium channels</td>
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<td></td>
<td>Other autoantibodies</td>
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<td></td>
<td>Systemic lupus erythematosus</td>
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<td>Hereditary sensory and autonomic neuropathies</td>
<td>Type I autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Type II autosomal recessive (Morvan disease)</td>
</tr>
<tr>
<td></td>
<td>Type III autosomal recessive (Riley-Day)</td>
</tr>
<tr>
<td></td>
<td>Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis)</td>
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<td></td>
<td>Type V absence of pain</td>
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<td>Metabolic</td>
<td>Fabry disease</td>
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<td>Diabetes mellitus</td>
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<td>Chagas disease</td>
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<td>Botulism</td>
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<td></td>
<td>Leprosy</td>
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<td></td>
<td>Diphtheria</td>
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<tr>
<td>Other</td>
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<td></td>
<td>Navajo Indian neuropathy</td>
</tr>
<tr>
<td></td>
<td>Multiple endocrine neoplasia type 2b</td>
</tr>
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<td></td>
<td>Toxins (see Table 614-1 in Chapter 614)</td>
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hereditary sensory-autonomic neuropathies (HSANs). Table 615-3 lists autonomic nervous system functional tests. The general treatment of acquired autonomic dysfunction includes treating the primary disorder (systemic lupus erythematosus, diabetes) and long-term management of specific organ system manifestations (Table 615-4). Acute fluctuations of autonomic symptoms may be seen in Guillain-Barré syndrome. Rapid fluctuations of hypertension or tachycardia changing to hypotension or bradycardia should be managed carefully and with very short-acting medications.

615.1 Familial Dysautonomia
Harvey B. Sarnat

Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive disorder that is common in Eastern European Jews, among whom the incidence is 1 in 10,000-20,000, and the carrier state is estimated to be 1%. It is rare in other ethnic groups but is the most common HSAN. The defective gene is at the 9q31-q33 locus. The familial dysautonomia gene is identified as IKBKAP (IκB kinase–associated protein), with aberrant splicing and a truncated protein (see Table 615-2). This and other autonomic neuropathies are often regarded as neurocristopathies because the abnormal target tissues are largely derived from neural crest.
in the 1st 5 yr of life. Episodic arterial hypertension and hypotension may be related to loss of baroreceptor modulation of muscle vasoco- strictor drive, and an acute fall in blood pressure manifests as ortho- static hypotension. Chronic and progressive renal disease may result from renal hypoperfusion. Responses to hypoxia are reduced.

As affected children become older, insensitivity to pain becomes evident and traumatic injuries are frequent. Pain and temperature sen- sation is reduced but is not as severe as in other HSANs (see Table 615-2). Corneal ulcerations are common partly as a result of decreased corneal reflexes and perhaps because of alacrima (absence of tears with emotional crying), which is a universal finding. Newly erupting teeth cause tongue ulcerations and, in older children, dental trauma and oral soft tissue mutilation may be prominent. Walking is delayed or clumsy or appears ataxic because of poor sensory feedback from muscle spin- dles. The ataxia is probably related more to deficient muscle spindle feedback and to vestibular nerve dysfunction than to cerebellar involve- ment, but defective ocular saccades also may indicate cerebellar dys- function and cerebellar atrophy. Tendon stretch reflexes are absent. Scoliosis or kyphosis is a serious complication in the majority of patients and usually is progressive. Overflow tearing with crying does not normally develop until 2-3 mo of age but fails to develop after that time or is severely reduced or absent in children with familial dysau- tonomia. There is an increased incidence of urinary incontinence. Bradycardia and other cardiac arrhythmias can occur, and some patients require a cardiac pacemaker.

Approximately 40% of patients have generalized major motor sei- zures; some of these are associated with acute hypoxia during breath- holding and some with extreme fevers, but most do not have an apparent precipitating event. Body temperature is poorly controlled; both hypothermia and extreme fevers occur. Impaired intellectual function is not secondary to epilepsy. Emotional lability and learning disabilities are common in school-age children with the disorder. Puberty is often delayed, especially in girls. Short stature can occur, but growth velocity can be accelerated by treatment with growth hormone. Speech is often slurred or nasal.

After 3 yr of age, autonomic crises begin, usually with attacks of cyclic vomiting lasting 24-72 hr or even several days. Retching and vomiting occur every 15-20 min and are associated with hypertension, profuse sweating, blotching of the skin, apprehension, and irritability. Prominent gastric distention can occur, causing abdominal pain and even respiratory distress. Hematopathy can complicate pernicious vomiting. Activation of dopamine receptors may explain the cyclic vomiting and retching.

Allgrove syndrome (triple A syndrome) is a clinical variant, involving early-onset alacrima, feeding difficulties and achalasia, auto- nomic dysfunction with orthostatic hypotension, altered heart rate variability, hyperreflexia, ataxia, muscle weakness, sensorimotor polyneuropathy, and adenocorticotrophic hormone–resistant adrenal insufficiency (develops in 1st decade). The gene AAAS (alacrima- achalasia-adrenal insufficiency neurologic disorder) is located on chromosome 12q13.

LABORATORY FINDINGS

Electrocardiography discloses prolonged corrected QT intervals with lack of appropriate shortening with exercise, a reflection of the aberration in autonomic regulation of cardiac conduction. Chest radio- graphs show atelectasis and pulmonary changes resembling cystic fibrosis. Urinary vanillylmandelic acid level is decreased, and the homovanillic acid level is increased. Plasma level of dopamine β-hydroxylase (the enzyme that converts dopamine to epinephrine) is diminished. Sural nerve biopsy shows a decreased number of unmyelinated fibers. Electroencephalography is useful for evaluating seizures.

DIAGNOSIS

Slow IV infusion of norepinephrine produces an exaggerated pressor response. The hypotensive response to infusion of methacholine is increased. Intradermal injection of 1:1,000 histamine phosphate fails to produce a normal axon flare, and local pain is absent or diminished.

**PATHOLOGY**

This disease of the peripheral nervous system is characterized patho- logically by a reduced number of small unmyelinated fiber networks that carry pain, temperature, and taste sensations and that mediate autonomic functions including baroreceptors. Large myelinated afferent nerve fibers that relay impulses from muscle spindles and Golgi tendon organs also are deficient. The degree of demonstrable anatomic change in peripheral and especially autonomic nerves is variable. Optic neu- ropathy with predominant loss of papillomacular nerve fibers may impair visual acuity. Fungiform papillae of the tongue (taste buds) are absent or reduced in number (Fig. 615-2). The number of parasympa- thetic ganglion cells in the myenteric plexuses is reduced. There is terminal vessel hyperperfusion in tissues, despite an overall hypoperfu- sion of organs and extremities.

**CLINICAL MANIFESTATIONS**

Clinical manifestations are highly variable between individuals. The disease is expressed in infancy by poor sucking and swallowing. Aspiration pneumonia can occur. Feeding difficulties with oral incoordina- tion is a major symptom throughout childhood. Vomiting crises can occur, and indeed nausea, retching, and hyperemesis (dysautonomic crisis) are the most disabling symptoms in some children. Apart from dysphagia, esophageal dysmotility can contribute to these symptoms. Episodic somnolence can occur in infants, as does hypotonia. Exces- sive sweating and blotchy erythema of the skin are common, especially at mealtime or when the child is excited. Infants are vulnerable to heatstroke. Episodic hyperhidrosis is caused by chemical hypersensi- tivity of the remaining sudomotor axons rather than of the sweat gland secretory cells. Breathholding spells followed by syncope are common.

**Figure 615-2**

A, Normal tongue with fungiform papillae present on the tip. B, Dysautonomic tongue. Note the absence of the highly vas- cularized fungiform papillae from the tongue tip, which gives the appearance of a smooth tongue. (From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV, Orphanet J Rare Dis 2:39, 2007, Fig. 4.)
Because the skin of a normal infant reacts more intensely to histamine, a 1:10,000 dilution should be used. Instillation of 2.5% methacholine into the conjunctival sac produces miosis in patients with familial dysautonomia and no detectable effect on a normal pupil; this is a nonspecific sign of parasympathetic denervation from any cause. Methacholine is applied to only 1 eye in this test, with the other eye serving as a control; the pupils are compared at 5 min intervals for 20 min. The combination of alacrima, absent fungiform papillae, decreased patellar reflexes, and an abnormal histamine test with Ashkenazi Jewish lineage is diagnostic. Because of variable expression and potential overlap with other HSANs, genetic testing should be used to confirm the diagnosis.

**TREATMENT**

Symptomatic treatment includes special attention to the respiratory and gastrointestinal systems to prevent aspiration and malnutrition, methylcellulose eyedrops or topical ocular lubricants to replace tears and prevent corneal ulceration, orthopedic management of scoliosis and joint problems, and appropriate anticonvulsants for epilepsy. Chlorpromazine is an effective antiemetic and may be given as rectal suppositories during autonomic crises; however, clonidine may be more effective. It also reduces apprehension and lowers the blood pressure. Diazepam has also been effective in some cases. Dehydration and electrolyte disturbances should be anticipated. A more specific and promising approach is the administration of carbidopa, an inhibitor of dopa-decarboxylase, particularly for the hyperemesis that is so prominent and disabling in many patients. Blockers of dopamine receptors are alternative drugs for cyclic vomiting. It is also useful for enuresis, another common complication, and augments tear production. Protection from injuries is important because of the lack of pain as a protective mechanism. Scoliosis often requires surgical treatment. Antiepileptic drugs may be required. A cardiac pacemaker may be required by some children. Blood pressure monitoring may be important in some cases. A promising genetic approach to treatment, which corrects the splicing defect, is the use of oral kinetin to regulate the expression of IKBKAP transcripts. Specific compounds identified from stem cells obtained from dysautonomia patients provide a potential therapy to rescue IKBKAP expression.

**PROGNOSIS**

Sixty percent of patients die in childhood before the age of 20 yr, usually of chronic pulmonary failure or aspiration. Treatment in a center familiar with the diverse complications greatly extends the life expectancy; some have survived to age 40 yr. Prevention of aspiration with fundoplication, gastrostomy, and tube feeding reduces the risk of aspiration. Newer measures to better control vasomotor stability and vomiting improve the quality of life, but whether they change longevity is not yet known.

**615.2 Other Autonomic Neuropathies**

*Harvey B. Sarnat*

**CONGENITAL INSENSITIVITY TO PAIN AND ANHIDROSIS**

Congenital insensitivity to pain and anhidrosis is an autosomal recessive disorder HSAN type IV (see Table 615-2). Onset is in infancy. Patients have episodes of extreme fevers related to warm environmental temperatures because they have absent or reduced sweating. Frequent burns and traumatic injuries result from apparent lack of pain perception. Poor healing of fractures occurs, as does osteomyelitis. Neonatal hypotonia improves with growth but learning problems may develop. Intelligence is normal. Nerve biopsy reveals an almost total absence of unmyelinated nerve fibers that convey impulses of pain, temperature, and autonomic functions. Some cases of hypomyelinating neuropathy manifest clinically as congenital insensitivity to pain (see Chapter 613.3). The sympathetic skin response as an electrophysiologic study is a reliable diagnostic test in cases associated with a mutation in the TrKA receptor for nerve growth factor.

**REFLEX SYMPATHETIC DYSTROPHY**

Reflex sympathetic dystrophy is a form of local causalgia, usually involving a hand or foot but not corresponding to the anatomic distribution of a peripheral nerve (see Chapter 168.2). A continuous burning pain and hyperesthesia are associated with vasomotor instability in the affected zone, resulting in increased skin temperature, erythema, and edema caused by vasodilation and hyperhidrosis. In the chronic state, atrophy of skin appendages, cool and clammy skin, and disuse atrophy of underlying muscle and bone occur. More than 1 extremity is occasionally involved. The pain is disabling and is exacerbated by the movement of an associated joint, although no objective signs of arthritis are seen; immobilization provides some relief. The most common preceding event is local trauma in the form of a contusion, laceration, sprain, or fracture that occurred days or weeks earlier.

Several theories of pathogenesis have been proposed to explain this phenomenon. The most widely accepted is reflexive overactivity of autonomic nerves in response to injury, and regional sympathetic blockade often affords temporary relief. Physiotherapy also is helpful. Some cases resolve spontaneously after weeks or months, but others continue to be symptomatic and require sympathectomy. A psychogenic component is suspected in some cases but is difficult to prove.

*Bibliography is available at Expert Consult.*
Bibliography
Bibliography


Guillain-Barré Syndrome

Guillain-Barré syndrome is an autoimmune disorder often considered a postinfectious polyneuropathy involving mainly motor but also sensory and sometimes autonomic nerves. This syndrome affects people of all ages and is not hereditary. Most patients in the United States and Europe have a demyelinating neuropathy, but primarily axonal degeneration is documented in some cases, mainly in China, Mexico, Bangladesh, and Japan.

**CLINICAL MANIFESTATIONS**

The paralysis usually follows a nonspecific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal (especially *Campylobacter jejuni*, but also *Helicobacter pylori*) or respiratory tract (especially *Mycoplasma pneumoniae*) symptoms. Consumption of undercooked poultry, unpasteurized milk, and contaminated water are the main sources of gastrointestinal infections. West Nile virus also can mimic Guillain-Barré–like syndrome, but more often it causes motor neuron disease similar to poliomyelitis. Guillain-Barré syndrome is reported following administration of vaccines against rabies, influenza, and poliomyelitis (oral) and following administration of conjugated meningococcal vaccine, particularly serogroup C. Additional infectious precursors of Guillain-Barré syndrome include mononucleosis, Lyme disease, cytomegalovirus, and *Haemophilus influenzae* (for the Miller-Fisher syndrome).
Initial symptoms include numbness and paresthesia, followed by weakness. There may be associated neck, back, buttock, and leg pain. Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and, finally, the bulbar muscles, a pattern known as Landry ascending paralysis. Proximal and distal muscles are involved relatively symmetrically, but asymmetry is found in 9% of patients. The onset is gradual and progresses over days or weeks; the process plateaus in 1-28 days. Particularly in cases with an abrupt onset, tenderness on palpation and pain in muscles are common in the initial stages. Affected children are irritable. Weakness can progress to inability or refusal to walk and later to flaccid tetraplegia. Maximal severity of weakness is usually reached by 4 wk after onset. The differential diagnosis of acute weakness is noted in Table 607-3 (in Chapter 607) and of Guillain-Barré syndrome in Table 616-1.

Bulbar involvement occurs in about half of cases. Respiratory insufficiency can result. Dysphagia and facial weakness are often impending signs of respiratory failure. They interfere with eating and increase the risk of aspiration. The facial nerves may be involved. Some young patients exhibit symptoms of viral meningitis or meningoencephalitis. Extraocular muscle involvement is rare, but in an uncommon variant, oculomotor and other cranial neuropathies are severe early in the course.

Miller-Fisher syndrome (MFS) consists of acute external and occasionally internal ophthalmoplegia, ataxia, and areflexia. The 6th cranial nerve is most often involved in MFS. Papilledema may precede or follow MFS and suggests a diagnosis of pseudotumor; optic neuritis may also be noted. Although areflexia is seen in MFS, patients do not have significant lower extremity weakness compared with Guillain-Barré syndrome. Distal paresthesias are noted in MFS. Urinary incontinence or retention of urine is a complication in approximately 20% of cases but is usually transient. MFS overlaps with Bickerstaff brainstem encephalitis, which also shares many features with Guillain-Barré syndrome with lower motor neuron involvement.

Tendon reflexes in Guillain-Barré syndrome are lost, usually early in the course, but are sometimes preserved until later; areflexia is common but hyporeflexia may be seen; 10% may have normal reflexes. This variability can cause confusion when attempting early diagnosis. The autonomic nervous system is also involved in some cases. Lability of blood pressure and cardiac rate, postural hypotension, episodes of profound bradycardia, or tachycardia and occasional asystole occur. Cardiovascular monitoring is important. A few patients require insertion of a temporary venous cardiac pacemaker.

Subtypes of Guillain-Barré syndrome include an acute inflammatory demyelinating polyneuropathy and an acute motor axonal neuropathy; these are distinguished by nerve conduction studies, geography, and the pattern of antiganglioside antibodies (Table 616-2). Localized forms also occur and include a pattern of facial palsy with paresthesias and a pattern of pharyngeal-cervical-brachial weakness.

Chronic inflammatory demyelinating polyradiculoneuropathies (CIDPs, sometimes called chronic inflammatory relapsing polyneuritis or chronic unremitting polyradiculoneuropathy) are chronic varieties of Guillain-Barré syndrome that recur intermittently, or do not improve, or progress slowly and relentlessly for periods of months to years. Approximately 7% of children with Guillain-Barré syndrome suffer an acute relapse. Patients are usually severely weak and can have a flaccid tetraplegia with or without bulbar and respiratory muscle involvement. Hyporeflexia or areflexia is almost universal. Motor deficits occur in 94% of cases, sensory paresthesias in 64%, and cranial nerve involvement in less than a third of patients. Autonomic and micturitional involvement is variable. Cerebrospinal fluid (CSF) shows no pleocytosis and protein is variably normal or mildly elevated. Nerve conduction

### Table 616-1

<table>
<thead>
<tr>
<th>SPINAL CORD LESIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute transverse myelitis</td>
</tr>
<tr>
<td>Epidural abscess</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Poliomyelitis (natural or live virus)</td>
</tr>
<tr>
<td>Enteroviruses</td>
</tr>
<tr>
<td>Hopkins syndrome</td>
</tr>
<tr>
<td>Vascular malformations</td>
</tr>
<tr>
<td>Cord infarction</td>
</tr>
<tr>
<td>Fibrocartilaginous embolism</td>
</tr>
<tr>
<td>Cord compression from vertebral subluxation related to congenital abnormalities or trauma</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
</tr>
<tr>
<td>Bickerstaff brainstem encephalitis for Miller-Fisher syndrome</td>
</tr>
</tbody>
</table>

### PERIPHERAL NEUROPATHIES

- Toxic
  - Vincristine
  - Glue sniffing
  - Heavy metal: gold, arsenic, lead, thallium
  - Organophosphate pesticides
  - Fluoroquinolones
  - Infections
    - HIV
    - Diphtheria
    - Lyme disease
  - Inborn errors of metabolism
  - Leigh disease
  - Tangier disease
  - Porphyria
  - Critical illness: polyneuropathy/myopathy
  - Vasculitis syndromes
  - Porphyria
  - Mitochondrial neurogastrointestinal encephalomyopathy
  - CD59 deficiency

### NEUROMUSCULAR JUNCTION DISORDERS

- Tick paralysis
- Myasthenia gravis
- Botulism
- Hypercalcemia
- Myopathies
- Periodic paralyses
- Dermatomyositis
- Critical illness myopathy/polyneuropathy


### Table 616-2

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute motor and sensory axonal neuropathy</td>
<td>GM1, GM1b, GD1a</td>
</tr>
<tr>
<td>Acute motor axonal neuropathy</td>
<td>GM1, GM1b, GD1a, GalNac-GD1a</td>
</tr>
<tr>
<td>Acute sensory neuronopathy</td>
<td>GD1a</td>
</tr>
<tr>
<td>ACUTE PANDYSAUTONOMIA</td>
<td></td>
</tr>
<tr>
<td>Regional Variants</td>
<td></td>
</tr>
<tr>
<td>Fisher syndrome</td>
<td>GQ1b, GT1a</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>GT1a</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>GQ1b, GM1, GM1b, GD1a, GalNac-GD1a</td>
</tr>
</tbody>
</table>

velocity studies and sural nerve biopsy are abnormal. Polymorphic nucleotide repeats in the \textit{SH2D2A} gene are associated with a predisposition to CIDP.

**Congenital Guillain-Barré syndrome** is described rarely, manifesting as generalized hypotonia, weakness, and areflexia in an affected neonate, fulfilling all electrophysiologic and CSF criteria and in the absence of maternal neuromuscular disease. Treatment might not be required, and there is gradual improvement over the 1st few mo and no evidence of residual disease by 1 yr of age. In 1 case, the mother had ulcerative colitis treated with prednisone and mesalamine from the 7th mo of gestation until delivery at term.

**LABORATORY FINDINGS AND DIAGNOSIS**

CSF studies are essential for diagnosis. The CSF protein is elevated to more than twice the upper limit of normal, the glucose level is normal, and there is no pleocytosis. Fewer than 10 white blood cells/mm$^3$ may be found. The results of bacterial cultures are negative, and viral cultures rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response in a patient with an acute or subacute polyneuropathy is diagnostic of Guillain-Barré syndrome. MRI of the spinal cord may be indicated to rule out disorders listed in Table 616-1. MRI findings include thickening of the cauda equina and intrathecal nerve roots with gadolinium enhancement. These findings are fairly sensitive and are present in >90% of patients (Fig. 616-1). Imaging in CIDP is similar but demonstrates greater enhancement of spinal nerve roots (Fig. 616-2).

Motor nerve conduction velocities are greatly reduced, and sensory nerve conduction time is often slow. Electromyography shows evidence of acute denervation of muscle. Serum creatine kinase level may be mildly elevated or normal. Antiganglioside antibodies, mainly against GM$_1$ and GD$_3$, are sometimes elevated in the serum in Guillain-Barré syndrome, particularly in cases with primarily axonal rather than demyelinating neuropathy, and suggest that they might play a role in disease propagation and/or recovery in some cases (see Table 616-1). Muscle biopsy is not usually required for diagnosis; specimens appear normal in early stages and show evidence of denervation atrophy in chronic stages. Sural nerve biopsy tissue shows segmental demyelination, focal inflammation, and wallerian degeneration but also is usually not required for diagnosis.

Serologic testing for 	extit{Campylobacter} and 	extit{Helicobacter} infections helps establish the cause if results are positive but does not alter the course of treatment. Results of stool cultures are rarely positive because

**Figure 616-1** Guillain-Barré syndrome. Sagittal off-midline (A) and midline (B) postgadolinium T1-weighted fat-saturated images through the lumbar spine of a patient who could not ambulate. C and D, Axial postcontrast T1-weighted images through the conus medullaris and proximal lumbar nerve roots, respectively. The images show extensive contrast enhancement of nerve roots (arrows in A–D), in keeping with changes of Guillain-Barré. (From Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 65-6.)
Even if *C. jejuni* infection is documented by stool culture or serologic tests, treatment of the infection is not necessary because it is self-limited, and the use of antibiotics does not alter the course of the polyneuropathy.

For the treatment of chronic neuropathic pain following Guillain-Barré syndrome, gabapentin is more effective than carbamazepine, and the requirement for fentanyl is reduced. But no pharmacologic treatments for neuropathic pain in this disease are wholly effective.

**PROGNOSIS**

The clinical course is usually benign, and spontaneous recovery begins within 2-3 wk. Most patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient opposite the direction of involvement: bulbar function recovering first, and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement can lead to death if the syndrome is not recognized and treated. Although prognosis is generally good and the majority of children recover completely, 3 clinical features are predictive of poor outcome with sequelae: cranial nerve involvement, intubation, and maximum disability at the time of presentation. The electrophysiologic features of conduction block are predictive of good outcome. Long-term follow-up studies of patients who recover from an attack of Guillain-Barré syndrome reveal that many do have some permanent axonal loss, with or without residual clinical signs of chronic neuropathy. Easy fatigue is one of the most common chronic symptoms, but it is not the rapid fatigability of muscles seen in myasthenia gravis. Most patients with the axonal form of Guillain-Barré syndrome had a slow recovery over the 1st 6 mo and could eventually walk, although some required years to recover. Electromyography and nerve conduction velocity electrophysiologic studies do not necessarily predict the long-term outcome.

**TREATMENT**

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles during the next 24 hr. Respiratory effort (negative inspiratory force, spirometry) must be monitored to prevent respiratory failure and respiratory arrest. Patients with slow progression might simply be observed for stabilization and spontaneous remission without treatment. Rapidly progressive ascending paralysis is treated with intravenous immunoglobulin (IVIG), administered for 2, 3, or 5 days. A commonly recommended protocol is IVIG 0.4 g/kg/day for 5 consecutive days, but some studies suggest that larger doses are more effective (1 g/kg/day for 2 consecutive days) and related to improved outcome. Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are not effective. Supportive care, such as respiratory support, prevention of decubiti in children with flaccid tetraplegia, nutritional support, pain management, prevention of deep vein thrombosis, and treatment of secondary bacterial infections, is important.

CIDPs, whether relapsing-remitting or unremitting, also are treated with oral or pulsed steroids and IVIG. Subcutaneous immunoglobulin infusion may be an alternative to the intravenous route. Plasma exchange, sometimes requiring as many as 10 exchanges daily, is an alternative. Remission in these cases may be sustained, but relapses can occur within days, weeks, or even after many months; relapses usually respond to another course of plasmapheresis. Steroid and immunosuppressive drugs are another alternative, but their effectiveness is less predictable. High-dose pulsed methylprednisolone given intravenously is successful in some cases. The prognosis in chronic forms of the Guillain-Barré syndrome is more guarded than in the acute form, and many patients are left with major residual handicaps.

Even if *C. jejuni* infection is documented by stool culture or serologic tests, treatment of the infection is not necessary because it is self-limited, and the use of antibiotics does not alter the course of the polyneuropathy.

For the treatment of chronic neuropathic pain following Guillain-Barré syndrome, gabapentin is more effective than carbamazepine, and the requirement for fentanyl is reduced. But no pharmacologic treatments for neuropathic pain in this disease are wholly effective.

**Figure 616-2** Chronic inflammatory demyelinating polyneuropathy (CIDP) in a 13 yr old boy with peripheral neuropathy and gait disturbance. Sagittal fat-saturated T1-weighted images off the midline to the right (A), at the midline (B), and off the midline to the left (C). (From Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 65-7.)
Bell Palsy
Harvey B. Sarnat

Bell palsy is an acute unilateral peripheral facial nerve palsy that is not associated with other cranial neuropathies or brainstem dysfunction. It is a common disorder at all ages from infancy through adolescence and usually develops abruptly within 2 wk after a systemic viral infection. The preceding infection is caused by the herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, Lyme disease, mumps virus, Toxocara, Rickettsia, Mycoplasma, or HIV infection (Table 617-1). Ramsay Hunt syndrome (herpes zoster oticus) is associated with vesicles in the external auditory canal or auricle and an ipsilateral facial palsy. Active or reactivation of herpes simplex or varicella-zoster virus may be the most common cause of Bell palsy (Fig. 617-1). The disease is occasionally a postinfectious allergic or immune demyelinating facial neuritis. It also may be a focal toxic or inflammatory neuropathy and has been associated with ribavirin and interferon-α therapy for hepatitis C. Hereditary forms are rare, but it may be associated with other genetic polyneuropathies. Rarely, Bell palsy occurs in the context of hypertension or juvenile type 1 diabetes mellitus, most often associated with concomitant viral infections.

**Table 617-1 Etiologies of Acute Peripheral Facial Palsy**

<table>
<thead>
<tr>
<th>COMMON</th>
<th>OTHER LESS-COMMON CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Trauma</td>
</tr>
<tr>
<td>Herpes simplex virus type 1*</td>
<td>Schwannoma of facial nerve</td>
</tr>
<tr>
<td>Varicella-zoster virus*</td>
<td>Infiltrative tumor</td>
</tr>
<tr>
<td><strong>LESS-COMMON INFECTIONS</strong></td>
<td>Aneurysm or vascular</td>
</tr>
<tr>
<td>Otitis media ± cholesteatoma</td>
<td>malformation</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Anomalous narrowing of facial</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>canal</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Mumps</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>Diabetes mellitus, type 1</td>
</tr>
<tr>
<td>Intranasal influenza vaccine</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Toxocara</td>
<td>Melkerson-Rosenthal syndrome</td>
</tr>
<tr>
<td>Rickettsia</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>Interferon</td>
</tr>
</tbody>
</table>

*Implicated in idiopathic Bell palsy.

Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

**Figure 617-1 Involvement of herpes simplex and varicella-zoster viruses in acute facial palsy.** (Modified from Hato N, Murakami S, Gyö K: Steroid and antiviral treatment for Bell’s palsy, Lancet 371:1818–1820, 2008.)

**CLINICAL MANIFESTATIONS**

The upper and lower portions of the face are paretic, and the corner of the mouth droops. Patients are unable to close the eye on the involved side and can develop an exposure keratitis at night. Taste on the anterior two thirds of the tongue is lost on the involved side in approximately 50% of cases; this finding helps to establish the anatomic limits of the lesion as being proximal or distal to the chorda tympani branch of the facial nerve. Nummness and paresthesias do not usually occur, but ipsilateral numbness of the face is reported in a few cases and probably is caused by viral (especially herpes) or postviral immunologic impairment of the trigeminal and the facial nerves. Pain behind the ear may precede weakness. Acute hearing loss may occur in Bell palsy associated with *Rickettsia* infection. Several grading systems have been devised for Bell palsy, including the Sunnybrook, House-Brackmann, and Yanagihara systems.

**IMAGING THE FACIAL NERVE AND ITS BONY CANAL**

Modern high-resolution MRI, particularly with multiplanar reconstruction, is able to visualize the facial nerve within its canal and determine whether there are bony anomalies, compressive aneurysms, vascular malformations, or nerve sheath or infiltrative tumors that might explain a palsy anatomically. The two sides can be compared and, in particular, the labyrinthine segment within the petrous bone, which is the narrowest site in the facial nerve canal, can be examined. Ultrasound of the facial nerve also has been used, in part as a predictor of functional outcome in Bell palsy. More recently, diffusion tensor tractography enables a tridimensional display of facial nerve axons.

**TREATMENT**

Oral prednisone (1 mg/kg/day for 1 wk, followed by a 1 wk taper) started within the 1st 3-5 days results in improved outcome and is a traditional treatment, its efficacy confirmed in a recent long-term prospective study in the United Kingdom. Because of the recovery of herpes simplex virus in the neural fluid of the 7th nerve, some also recommend adding oral acyclovir or valacyclovir to the prednisone therapy. Alone, antiviral agents are not effective in reducing adverse sequelae (synkinesis, autonomic dysfunction), but added to prednisone may be associated with an additional small benefit. If a specific infection can be identified as a predisposing cause, specific antiviral or antibacterial treatment is more justified. Surgical decompression of the facial canal, theoretically to provide more space for the swollen facial nerve, is not of value unless imaging provides evidence of nerve compression or an anatomic lesion. Both high- and low-level laser therapy has been used with good results in some cases as a form of physiotherapy. Traditional physiotherapy to the facial muscles is recommended in some chronic cases with poor recovery, but the efficacy of this treatment is uncertain. Protection of the cornea with methylcellulose eyedrops or an ocular lubricant is especially important at night. Botulinum toxin has been applied in adults to the contralateral normal facial muscles for cosmetic purposes to minimize the apparent asymmetry or to treat chronic unilateral ptosis, but this has little application in pediatric patients.

**PROGNOSIS**

The prognosis for functional recovery is excellent. More than 85% of patients recover spontaneously with no residual facial weakness. Another 10% have mild facial weakness as a sequela, often perceived only as a mild facial asymmetry, and only 5% are left with permanent severe facial weakness. In patients who do not recover within a few weeks (chronic), electrophysiologic examination of the facial nerve helps to determine the degree of neuropathy and regeneration. In chronic cases, other causes of facial neuropathy should be considered, including facial nerve tumors such as schwannomas and neurofibromas, infiltration of the facial nerve by leukemic cells or by a rhabdomyosarcoma of the middle ear, brainstem infarcts or tumors, and traumatic injury of the facial nerve.

Nerve regrowth may be misdirected and result in *synkinesis*, where activation of one muscle group may produce activation of another.
inappropriate muscle group; blinking may result in mouth twitching, smiling may cause eye blinking, and lacrimation (crocodile tears) may occur while eating.

**FACIAL PALSY AT BIRTH**

Facial palsy at birth is usually a compression neuropathy from forceps application during delivery and recovers spontaneously in a few days or weeks in most cases. **Congenital absence of the depressor angularis oris muscle** causes facial asymmetry, especially when an affected infant cries, and is often associated with other congenital anomalies, especially of the heart. It is not a facial nerve lesion but is a cosmetic defect that does not interfere with feeding. Infants with Möbius syndrome can have bilateral or, less commonly, unilateral facial palsy; this syndrome is usually caused by symmetric calcified infarcts in the tegmentum of the pons and medulla oblongata during midgestation or late fetal life, although it rarely is a developmental anomaly of the brainstem.

*Bibliography is available at Expert Consult.*
Bibliography


The eye of a normal full-term infant at birth is approximately 65% of adult size. Postnatal growth is maximal during the 1st yr, proceeds at a rapid, but decelerating rate until the 3rd yr, and continues at a slower rate thereafter until puberty, after which little change occurs. The anterior structures of the eye are relatively large at birth but thereafter grow proportionately less than the posterior structures. This results in a progressive change in the shape of the globe such that it becomes more spherical.

In an infant, the sclera is thin and translucent, with a bluish tinge. The cornea is relatively large in newborns (averaging 10 mm) and attains adult size (nearly 12 mm) by the age of 2 yr or earlier. Its curvature tends to flatten with age, resulting in a progressive change in the refractive properties of the eye. A normal cornea is perfectly clear. In infants born prematurely, however, the cornea may have a transient opalescent haze. The anterior chamber in a newborn appears shallow, and the angle structures, important in the maintenance of normal intraocular pressure, must undergo further differentiation after birth. The iris, typically light blue or gray at birth in white individuals, undergoes progressive change of color as the pigmentation of the stroma increases in the 1st 6 mo of life. The pupils of a newborn infant tend to be small and are often difficult to dilate. This is the result of an immature iris dilator muscle. Remnants of the pupillary membrane (anterior vascular capsule) are often evident on ophthalmoscopic examination, appearing as cobweb-like lines crossing the pupillary aperture, especially in preterm infants.

The lens of a newborn infant is more spherical than that of an adult; its greater refractive power helps to compensate for the relative shortness of the young eye. The lens continues to grow throughout life; new fibers added to the periphery continually push older fibers toward the center of the lens. With age, the lens becomes progressively denser and more resistant to change of shape during accommodation.

The fundus of a newborn's eye is less pigmented than that of an adult; the choroidal vascular pattern is highly visible, and the retinal pigment pattern often has a fine peppy or motiled appearance. In some darkly pigmented infants, the fundus has a gray or opalescent sheen. In a newborn, the macular landmarks, particularly the foveal light reflex, are less well defined and may not be readily apparent. The peripheral retina appears pale or grayish, and the peripheral retinal vasculature is immature, especially in premature infants. The optic nerve head color varies from pink to slightly pale, sometimes grayish. Within 4-6 mo, the appearance of the fundus approximates that of the mature eye.

Superficial retinal hemorrhages may be observed in many newborn infants. These are usually absorbed promptly and rarely leave any permanent effect. The majority of birth-related retinal hemorrhages resolve within 2 wk, with complete resolution of all such hemorrhages within 4-6 wk of birth. Conjunctival hemorrhages also may occur at birth and are resorbed spontaneously without consequence.

Remnants of the primitive hyaloid vascular system may also be seen as small tufts or wormlike structures projecting from the disc (Bergmeister papilla) or as a fine strand traversing the vitreous; in some cases, only a small dot (Mittendorf dot) remains on the posterior aspect of the lens capsule.

An infant’s eye is somewhat hyperopic (farsighted). The general trend is for hyperopia to increase from birth until age 7 yr. Thereafter, the level of hyperopia tends to decrease rapidly until age 14 yr. Elimination of the hyperopic state may occur during this time. If the process continues, myopia (nearsightedness) develops. A slower continuation of the decrease in hyperopia, or increase in myopia, continues into the 3rd decade of life. The refractive state at any time in life depends on the net effect of many factors: the size of the eye, the state of the lens, and the curvature of the cornea.

Newborn infants tend to keep their eyes closed much of the time, but normal newborns can see, respond to changes in illumination, and fixate points of contrast. The visual acuity in newborns is estimated to be approximately 20/400. This poor vision is a result of the immature, multilayered foveal anatomy. Retinal development continues postnatally, maturing completely during the 1st few yr of life. One of the earliest responses to a formed visual stimulus is an infant’s regard for the mother’s face, evident especially during feeding. By 2 wk of age, an infant shows more sustained interest in large objects, and by 8-10 wk of age, a normal infant can follow an object through an arc of 180 degrees. The acuity improves rapidly and may reach 20/30-20/20 by the age of 2-3 yr.

Many normal infants may have imperfect coordination of the eye movements and alignment during the early days and weeks, but proper coordination should be achieved by 3-6 mo, usually sooner. Persistent deviation of an eye in an infant at 6 mo of age requires evaluation.

Tears often are not present with crying until after 1-3 mo. Preterm infants have reduced reflex and basal tear secretion, which may allow topically applied medications to become concentrated and lead to rapid drying of their corneas.

Bibliography is available at Expert Consult.
Bibliography


The eye exam is a routine part of the pediatric wellness evaluation, which begins in the newborn period. The primary care physician plays a critical role in the detection of both obvious and insidious, asymptomatic eye diseases. School and community screening programs can also be effective in identifying problems at an early age. The American Academy of Ophthalmology recommends preschool vision screening as a means of reducing preventable visual loss (Table 619-1). The screening process begins with the pediatrician during well child visits. Referrals to an ophthalmologist should be made when a significant ocular abnormality or visual acuity deficit is suspected. An
## Table 619-1  Vision Screening Guidelines

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>RECOMMENDED TESTS</th>
<th>REFERRAL CRITERIA</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGES 3-5 YR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distance visual acuity</strong></td>
<td>Snellen letters, Snellen numbers, Tumbling E test, HOTV test</td>
<td>&lt;4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., &lt;10/20 or 20/40), or Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and 10/20 or 20/25 and 20/40)</td>
<td>Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older.</td>
</tr>
<tr>
<td></td>
<td>Picture tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Allen figures, -Lea symbols</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ocular alignment</strong></td>
<td>Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)</td>
<td>Any eye movement</td>
<td>Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2-3 ft away; detects asymmetric refractive errors as well.</td>
</tr>
<tr>
<td></td>
<td>Simultaneous red reflex test (Bruckner test)</td>
<td>&lt;4 of 6 correct</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any asymmetry of pupil color, size, brightness</td>
<td></td>
</tr>
<tr>
<td><strong>Ocular media clarity</strong> (cataracts, tumors, etc.)</td>
<td>Red reflex</td>
<td>White pupil, dark spots, absent reflex                                             Direct ophthalmoscope, darkened room. View eyes separately at 12-18 inches; white reflex indicates possible retinoblastoma.</td>
<td></td>
</tr>
<tr>
<td><strong>AGES 6 YR AND OLDER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distance visual acuity</strong></td>
<td>Snellen letters, Snellen numbers, Tumbling E test, HOTV test</td>
<td>&lt;4 of 6 correct on 4.5 m (15 ft) line with either eye tested at 3 m (10 ft) monocularly (i.e., &lt;10/15 or 20/30)</td>
<td>Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older.</td>
</tr>
<tr>
<td></td>
<td>Picture tests</td>
<td>Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30)</td>
<td>Testing distance of 3 m (10 ft) is recommended for all visual acuity tests.</td>
</tr>
<tr>
<td></td>
<td>-Allen figures, -Lea symbols</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ocular alignment</strong></td>
<td>Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)</td>
<td>Any eye movement</td>
<td>A line of figures is preferred over a single figure. The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner must ensure that it is not possible to peek with the nontested eye.</td>
</tr>
</tbody>
</table>

Visual acuity

There are various means of assessing visual acuity in the pediatric population. A child's age and ability to cooperate, as well as clinician preference, all factor in deciding which test to use. The most common visual acuity test in infants is an assessment of their ability to fixate and follow a target. If appropriate targets are used, this response can be demonstrated by approximately 6 wk of age.

The test begins by seating the child comfortably in the caretaker’s lap. The object of visual interest, usually a bright-colored toy, or target with lights, is slowly moved to the right and to the left. The examiner observes whether the infant’s eyes turn toward the object and follow its movements. The examiner can use a thumb or palm of the hand to...
occlude one of the infant's eyes, in order to test each eye separately. Although a sound-producing object might compromise the purity of the visual stimulus, in practice, toys that squeak or rattle heighten an infant's awareness and interest in the test.

The human face is a better target than test objects. The examiner can exploit this by moving his or her face slowly in front of the infant's face. If the appropriate following movements are not elicited, the test should be repeated with the caretaker's face as the test stimulus. It should be remembered that even children with poor vision can follow a large object without apparent difficulty, especially if only 1 eye is affected.

An objective measurement of visual acuity is usually possible when children reach the age of 2.5-3 yr. Children this age are tested using a schematic picture or other illiterate eye chart. Examples include Allen or Lea symbols and tumbling E. Each eye should be tested separately. It is essential to prevent peeking. The examiner should hold the occluder in place and observe the child throughout the test. The child should be reassured and encouraged throughout the test as many children are intimidated by the process and fear a "bad grade" or punishment for errors.

The tumbling E test, in which the child indicates which direction the E is facing, is the most widely used visual acuity test for preschool children. Right–left presentations are more confusing than up–down presentations. With pretest practice, the test can be performed by most children ages 3-4 yr.

An adult-type Snellen acuity chart can be used at 5-6 yr of age if the child knows letters. A visual acuity of 20/40 is generally accepted as normal for 3 yr old children. At 4 yr of age, 20/30 is acceptable. By 5 or 6 yr of age, most children attain 20/20 vision.

Optokinetic nystagmus (the response to a sequence of moving targets; "railroad" nystagmus) can also be used to assess vision; this can be calibrated by targets of various sizes (stripes or dots) or by a rotating drum (known as an OKN drum) at specified distances.

The visual evoked response, an electrophysiologic method of evaluating the response to light and special visual stimuli, such as calibrated stripes or a checkerboard pattern, can also be used to study visual function in selected cases. Preferential looking tests are used for evaluating vision in infants and children who cannot respond verbally to standard acuity tests. This is a behavioral technique based on the observation that, given a choice, an infant prefers to look at patterned rather than unpatterned stimuli. Because these tests require the presence of a skilled examiner, their use is often limited to research protocols involving preverbal children.

VISUAL FIELD ASSESSMENT
Like visual acuity testing, visual field assessment must be geared to a child's age and abilities. Formal visual field examination (perimetry and scotomometry) can often be accomplished in school-age children. In younger children and in the pediatrician's office, the examiner must often rely on confrontation techniques and finger counting in quadrants of the visual field. In many such children, only testing by attraction can be accomplished; the examiner observes a child's response to familiar objects brought into each of the 4 quadrants of the visual field of each eye in turn. The child's bottle, a favorite toy, and lollipops are particularly effective attention-getting items. These gross methods can often detect diagnostically significant field changes such as the bitemporal hemianopia of a chiasmal lesion or the homonymous hemianopia of a cerebral lesion.

COLOR VISION TESTING
Color vision testing can be accomplished when a child is able to name or trace the test symbols, which include numbers, shapes, or other symbols. The common color vision testing tools include Ishihara color plates or Hardy Rand Littler. Color vision testing is not frequently necessary in young children; however, parents may request testing, particularly if their child seems to be slow in learning colors or if there is a family history of color vision deficiency. It is important to keep in mind, and reassure parents that "color-deficient" children do not misname colors, and that true "color blindness" is very rare and not compatible with normal vision. Defective color vision is common in male patients but rare in females, as the gene is transmitted in an X-linked manner. Achromatopsia, which may be encountered occasionally, is a condition of complete color blindness associated with subnormal visual acuity, nystagmus, and photophobia.

Color discrimination is a means of assessing the intensity of a hue, typically red. Patients describe the intensity of red depicted from the test object. A change in color discrimination (often referred to as color "desaturation") can be a sign of optic nerve or retinal disease.

PUPILLARY EXAMINATION
The pupil exam includes evaluations of both the direct and consensual responses to light, accommodation (a near target), and reduced illumination, noting the size and symmetry of the pupils under each testing condition. Special care must be taken to differentiate the reaction to light from the reaction to near gaze. A child's natural tendency is to look directly at the approaching light, inducing the near gaze reflex when one is attempting to test only the reaction to light; accordingly, every effort must be made to control fixation on a distance target. The swinging flashlight test is especially useful for detecting unilateral or asymmetric prechiasmatic afferent defects in children (see “Marcus Gunn Pupil” section in Chapter 622).

OCULAR MOTILITY
Ocular motility testing assesses alignment and extraocular muscle function. This is tested by having a child follow an object in various positions of gaze, known as the cardinal positions. The cardinal positions are those in which one extraocular muscle predominantly functions and a deficit can be identified if present. Movements of each eye individually (ductions) and of the 2 eyes together (versions, conjugate movements, and convergence) are assessed.

Alignment can be assessed in 2 ways. The first is symmetry of the corneal light reflexes. The second method is to occlude each eye in an alternating fashion and observe for a change in fixation of the viewing eye (see discussion on cover testing for strabismus in Chapter 623).

BINOCULAR VISION
Attaining binocular visual function is one of the primary goals of amblyopia therapy and ocular realignment surgery. Just as there are multiple methods for assessing visual acuity, there are various means of testing the level of binocular vision. The Titmus test is probably the most frequently used test; a series of three-dimensional images are shown to the child while he or she wears a set of polarized glasses. The level of difficulty with which these images can be detected correlates with the degree of binocular vision present.

EXTERNAL EXAMINATION
The external examination begins with general inspection, in good illumination of the face, paying close attention to the orbits and lids, noting the size, shape, and symmetry of the orbits; position and movement of the lids; and position and symmetry of the globes. Viewing the eyes and lids in such a manner aids in detecting orbital asymmetry, lid masses, proptosis (exophthalmos), and abnormal pulsations. Pupil is also important in detecting orbital and lid masses. Orbital dermoids and capillary hemangiomas are frequently evaluated during the external examination.

The lacrimal system is assessed by looking for evidence of tear deficiency, overflow of tears (epiphora), erythema, and swelling in the region of the tear sac or gland. The lacrimal gland is located in the superotemporal orbit, beneath the eyebrow. The tear drain system, which includes the lacrimal sac, is located within the medial wall of the orbit, where the eyelids meet the bridge of the nose. The sac is massaged to check for reflex when obstruction is suspected. The presence and position of the puncta are also checked.

The lids and conjunctivae are specifically examined for focal lesions, foreign bodies, and inflammatory signs; loss and misdirection of lashes should also be noted. When necessary, the lids can be everted in the following manner: (1) instruct the patient to look down; (2) grasp the lashes of the patient's upper lid between the thumb and index finger of 1 hand; (3) place a probe, a cotton-tipped applicator, or the thumb of
the other hand at the upper margin of the tarsal plate; and (4) pull the lid down and outward and evert it over the probe, using the instrument as a fulcrum. Foreign bodies commonly lodge in the concavity just above the lid margin and are exposed only by fully evertting the lid.

The anterior segment of the eye is then evaluated with oblique focal illumination, noting the luster and clarity of the cornea, the depth and clarity of the anterior chamber, and the features of the iris. Transillumination of the anterior segment aids in detecting opacities and in demonstrating atrophy or hypopigmentation of the iris; these latter signs are important when ocular albinism is suspected. When necessary, fluorescein dye can be used to aid in diagnosing abrasions, ulcerations, and foreign bodies.

**BIOMICROSCOPY (SLIT-LAMP EXAMINATION)**

The slit-lamp exam provides a highly magnified view of the various structures of the eye and an optical section through the media of the eye—the cornea, aqueous humor, lens, and vitreous. Lesions can be identified and localized according to their depth within the eye; the resolution is sufficient to detect individual inflammatory cells in the aqueous and anterior vitreous. With the addition of special lenses and prisms, the angle of the anterior chamber and components of the fundus also can be examined with a slit lamp. Biomicroscopy is often crucial in trauma and in examining for iritis. It is also helpful in diagnosing many metabolic and genetic diseases of childhood.

**FUNDUS EXAMINATION (OPHTHALMOSCOPY)**

The ideal setting for ophthalmoscopy is with a well-dilated pupil, unless there are neurologic or other contraindications. Tropicamide (Mydriacyl) 0.5-1% and phenylephrine (Neo-Synephrine) 2.5% are recommended as mydriatics of short duration. These are safe for most children, but the possibility of adverse systemic effects must be recognized. For very small infants, especially 6 mo or younger, more dilute preparations may be advisable. Beginning with posterior landmarks, the disc and the macula, the 4 quadrants are systematically examined by following each of the major vessel groups to the periphery. Retinal hemorrhages, vascular anomalies, and posterior uveitis are often appreciated during this segment of the examination. Color, cup, and contour of the optic nerve should be noted as well. Abnormalities are frequently followed with further imaging studies such as a CT or MRI or diagnostic testing such as automated perimetry (see “Visual Field Assessment” above). The midperipheral retina can be seen if a child is directed to look up and down and to the right and left. Even with care, only a limited fraction of the fundus can be seen with a direct or handheld ophthalmoscope. For examination of the far periphery, an indirect ophthalmoscope is used, and full dilation of the pupil is essential.

**REFRACTION**

Refraction determines the focusing power of the eye: the degree of nearsightedness (hypermetropia), farsightedness (myopia), or astigmatism. Retinoscopy provides an objective determination of the amount of correction needed and can be performed at any age, including the newborn period. In young children, it is best done with cycloplegia using cyclopentolate 1% eyedrops in an ophthalmologist’s office. Subjective refinement of refraction involves asking patients for preferences in the strength and axis of corrective lenses; it can be accomplished in many school-age children. Refraction and determination of visual acuity with appropriate corrective lenses in place are essential steps in deciding whether a patient has a visual defect or amblyopia. Photoscreening cameras aid ancillary medical personnel in screening for refractive errors in preverbal children. The accuracy and practical usefulness of these devices are still being investigated.

**TONOMETRY**

Tonometry is the method of assessing intraocular pressure. It may be performed with a portable, stand-alone instrument or by the applation method during slit-lamp examination. Alternative methods are pneumatic, electronic, or rebound tonometry. When accurate measurement of the pressure is necessary in a child who cannot cooperate,
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Chapter 620
Abnormalities of Refraction and Accommodation
Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

Emmetropia is the state in which parallel rays of light come to focus on the retina with the eye at rest (nonaccommodating). Even though such an ideal optical state is common, the opposite condition, ametropia, often occurs. Three principal types of ametropia exist: hyperopia (farsightedness), myopia (nearsightedness), and astigmatism (Fig. 620-1). The majority of children are physiologically hyperopic at birth. Yet a significant number, especially those born prematurely, are myopic and often have some degree of astigmatism. With growth the refractive state tends to change and should be evaluated periodically.

Measurement of the refractive state of the eye (refraction) can be accomplished both objectively and subjectively. The objective method involves directing a beam of light from a retinoscope onto a patient's retina. Using loose lenses of various strengths held in front of the eye, the retinal light reflex (viewed through the pupil) can be neutralized, yielding a precise refraction. An objective refraction is obtainable at any age because it requires no response from the patient. In infants and children, it is generally more accurate to perform a refraction after instillation of eyedrops that produce mydriasis (dilation of the pupil) and cycloplegia (paralysis of accommodation); those used most commonly are tropicamide (Mydriacyl), cyclopentolate (Cyclogyl), and atropine sulfate. A subjective refraction involves placing lenses in front of the eye and having the patient report which lenses provide the clearest image of the letters on a chart. This method is dependent on a patient's ability to discriminate and communicate, but can be used for some children and can be helpful in determining the best refractive correction for children who are developmentally capable.

HYPEROPIA
If parallel rays of light come to focus posterior to the retina with the eye in a neutral state, hyperopia or farsightedness exists. This may result from a shorter anteroposterior diameter of the eye or a lower refractive power of the cornea or lens.

In hyperopia, the additional refracting power needed to bring objects into focus at distance and near is generated through the accommodative mechanism. If the accommodative effort required for focus is within that child's accommodative amplitude, the vision is clear. In high degrees of hyperopia requiring greater accommodative effort, vision may be blurred, and the child may complain of eye strain, headaches, or fatigue. Squinting, eye rubbing, and lack of interest in reading are frequent manifestations. If the induced discomfort is great enough, a child may not make an effort to focus and may develop bilateral amblyopia (ametropic amblyopia). Esotropia may also be associated (see discussion on convergent strabismus, accommodative esotropia in Chapter 623). Convex lenses (spectacles or contact lenses) of sufficient
Disorders of the Eye

strength to provide clear vision and comfort are prescribed when indicated. Even children who have high degrees of hyperopia but who have good vision will happily wear glasses because they provide comfort by eliminating the excessive accommodation required to see well. Preverbal children should also be given glasses for high levels of hyperopia to prevent the development of esotropia or amblyopia. Children with normal levels of hyperopia do not require correction in the majority of cases.

MYOPIA

In myopia, parallel rays of light come to focus anterior to the retina. This is a result of either a long anteroposterior diameter of the eye or a higher refractive power of the cornea or lens. The principal symptom is blurred vision for distant objects. The far point of clear vision varies inversely with the degree of myopia; as the myopia increases, the far point of clear vision moves closer to the eye. With myopia of 1 diopter, for example, the far point of clear focus is 1 m from the eye; with myopia of 3 diopters, the far point of clear vision is only \( \frac{1}{3} \) m from the eye. Thus, myopic children tend to hold objects and reading material closer, prefer to be close to the blackboard, and may be uninterested in distant activities. Squinting is common because the visual acuity is improved when the lid aperture is reduced, also known as the pinhole effect.

Myopia is infrequent in infants and preschool-age children. It is more common in infants with a history of retinopathy of prematurity. A hereditary tendency to myopia is also observed, and children of myopic parents should be examined at an early age. The incidence of myopia increases during the school years, especially during the preteen and teen years. The degree of myopia also increases with age during the growing years.

Concave lenses (spectacles or contact lenses) of appropriate strength to provide clear vision and comfort are prescribed. Changes are usually needed periodically, from every few months to every 1-2 yr. Excessive accommodation during near work has been considered by some to lead to progression of myopia. Based on this philosophy, some practitioners advocate the use of cycloplegic agents, bifocals, intentional undercorrection of myopic refractive errors, or mandatory removal of myopic glasses for near work in an effort to retard the progression of myopia. The value of such treatment has not been scientifically proven.

Excimer laser correction for myopia has been approved for adults since 1995. The laser is applied to the corneal stroma to reshape the cornea, changing its refractive power. LASIK (laser-assisted in situ keratomileusis) uses either a microkeratome or a femtosecond laser to produce an epithelial-stromal flap permitting the underlying corneal
tissue to be ablated. The flap is then reseated and assumes the altered corneal shape. Photorefractive keratectomy (PRK) uses manual removal of the epithelium following treatment with alcohol to expose the Bowman layer and stroma, which is then treated by the excimer laser. The epithelium regenerates to cover the defect over a period of 4-10 days. Visual improvement is usually significant and remains stable over time. Risks are greatest with high degrees of myopia (>10 diopters) and include starbursts, halos, and distorted images or multiple images (usually at night). Refractive surgery is not approved for pediatric patients but is being used off-label to treat some forms of amblyopia and certain circumstances of myopia and astigmatism, usually by PRK.

In most cases, myopia is not a result of pathologic alteration of the eye and is referred to as simple or physiologic myopia. Some children may have pathologic myopia, a rare condition caused by a pathologically abnormal axial length of the eye; this is usually associated with thinning of the sclera, choroid, and retina and often with some degree of uncorrectable visual impairment. Tears or breaks in the retina may occur as it becomes increasingly thin, leading to the development of retinal detachments. Myopia may also occur as a result of other ocular abnormalities, such as keratoconus, ectopia lentis, congenital stationary night blindness, and glaucoma. Myopia is also a major feature of Stickler syndrome, a genetic disorder of connective tissue involving problems with vision, hearing, and facial and skeletal development.

ASTIGMATISM

In astigmatism, the refractive powers of the various meridians of the eye differ. Most cases are caused by irregularity in the curvature of the cornea, although some astigmatism results from changes in the lens. Mild degrees of astigmatism are common and may produce no symptoms. With greater degrees, distortion of vision can occur. To achieve a clearer image, a person with astigmatism uses accommodation or squints to obtain a pinhole effect. Symptoms include eyestrain, headache, and fatigue. Cylindrical or spherocylindrical lenses are used to provide optical correction when indicated. Glasses may be needed constantly or only part time, depending on the degree of astigmatism and the severity of the attendant symptoms. In some cases, contact lenses are used.

Infants and children with corneal irregularity resulting from injury, ptosis, or hemangiomas of the periorbita or eyelid are at increased risk of astigmatism and associated amblyopia.

ANISOMETROPIA

When the refractive state of one eye is significantly different from the refractive state of the other eye, anisometropia exists. If uncorrected, 1 eye may always be out of focus, leading to the development of amblyopia. Early detection and correction are essential if normal visual development in both eyes is to be achieved.

ACCOMMODATION

During accommodation, the ciliary muscle contracts, the suspensory fibers of the lens relax, and the lens assumes a more rounded shape, adding power to the lens. The amplitude of accommodation is greatest during childhood and gradually diminishes with age. The physiologic decrease in accommodative ability that occurs with age is called presbyopia.

Disorders of accommodation in children are relatively rare. Premature presbyopia is occasionally encountered in young children. The most common cause of paralysis of accommodation in children is intentional or inadvertent use of cycloplegic substances, topically or systemically; included are all the anticholinergic drugs and poisons, as well as plants and plant substances having these effects. Neurogenic causes of accommodative paralysis include lesions affecting the oculomotor nerve (3rd cranial nerve) in any part of its course. Differential diagnoses include tumors, degenerative diseases, vascular lesions, trauma, and infectious etiologies. Systemic disorders that may cause impairment of accommodation include botulism, diphtheria, Wilson disease, diabetes mellitus, and syphilis. Adie tonic pupil may also lead to a deficiency of accommodation after some viral illnesses (see Chapter 622). An apparent defect in accommodation may be psychogenic in origin; it is common for a child to feign inability to read when it can be demonstrated that visual acuity and ability to focus are normal.

Bibliography is available at Expert Consult.
Chapter 620 ♦ Abnormalities of Refraction and Accommodation

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Severe visual impairment (corrected vision poorer than 6/60) and blindness in children have many etiologies and may be caused by multiple defects affecting any structure or function along the visual pathways (Table 621-1). The overall incidence is approximately 2.5 per 100,000 children; the incidence is higher in developing countries, in low birthweight infants, and in the 1st yr of life. The most common causes occur during the prenatal and perinatal time periods; the cerebral-visual pathways, optic nerve, and retinal sites are most often affected. Important prenatal causes include autosomal recessive (most common), autosomal dominant, and X-linked genetic disorders as well as hypoxia and chromosomal syndromes. Perinatal/neonatal causes include retinopathy of prematurity, hypoxia–ischemia, and infection. Severe visual impairment starting in older children may be due to central nervous system or retinal tumors, infections, hypoxia–ischemia, injuries, neurodegenerative disorders, or juvenile idiopathic arthritis.

**AMBLYOPIA**

This is a decrease in visual acuity, unilateral or bilateral, that occurs in visually immature children as a result of a lack of a clear image projecting onto the retina. The unformed retinal image may occur secondary to a deviated eye (strabismic amblyopia), an unequal need for vision correction between the eyes (anisometropic amblyopia), a high refractive error in both eyes ( ametropic amblyopia), or a media opacity within the visual axis (deprivation amblyopia).

The development of visual acuity normally proceeds rapidly in infancy and early childhood. Anything that interferes with the formation of a clear retinal image during this early developmental period can produce amblyopia. Amblyopia occurs only during the critical period of development before the cortex has become visually mature, within the 1st decade of life. The younger the child, the more susceptible he or she is to the development of amblyopia.

The **diagnosis** of amblyopia is confirmed when a complete ophthalmologic examination reveals reduced acuity that is unexplained by an organic abnormality. If the history and ophthalmologic examination do not support the diagnosis of amblyopia in a child with poor vision, consideration must be given to other causes (neurologic, psychologic). Amblyopia is usually asymptomatic and can avoid detection until vision screening, which may delay diagnosis as screening programs often target school-age children. This is problematic as amblyopia is more resistant to treatment at an older age, being reversed more rapidly in younger children whose visual system is less mature. Thus, one key to the successful treatment of amblyopia is early detection and prompt intervention.

Most often **treatment** first consists of removing any media opacity or prescribing appropriate glasses, if needed, so that a well-focused retinal image can be produced in each eye. The sound eye is then
Table 621-1 Causes of Childhood Severe Visual Impairment or Blindness

<table>
<thead>
<tr>
<th>CONGENITAL</th>
<th>Special types: Dawson disease, Leigh disease, the Bassen-Kornzweig syndrome, Refsum disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic nerve hypoplasia or aplasia</td>
<td>Retinal degenerations: retinitis pigmentosa and its variants and Leber congenital type</td>
</tr>
<tr>
<td>Septooptic dysplasia</td>
<td>Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown</td>
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<td>Optic coloboma</td>
<td>INFECTIOUS/INFLAMMATORY PROCESSES</td>
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<td>Congenital hydrocephalus</td>
<td>Encephalitis, especially in the prenatal infection syndromes caused by Toxoplasma gondii, cytomegalovirus, rubella virus, Treponema pallidum, herpes simplex virus</td>
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<tr>
<td>Hydranencephaly</td>
<td>Meningitis; arachnoiditis</td>
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<td>Porencephaly</td>
<td>Chorioretinitis</td>
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<td>Micrencephaly</td>
<td>Endophthalmitis</td>
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<td>Encephalocele, particularly occipital</td>
<td>Trachoma</td>
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<td>Morning glory disc</td>
<td>Keratitis</td>
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<td>Rieger anomaly</td>
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<td>Cataracts</td>
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<td>Central retinal occlusion</td>
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<td>PHAKOMATOSESES</td>
<td>TRAUMA</td>
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<td>Tuberous sclerosis</td>
<td>Contusion or avulsion of optic nerves, chiasm, globe, cornea</td>
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<td>Neurofibromatosis (special association with optic glioma)</td>
<td>Cerebral contusion or laceration</td>
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<td>Sturge-Weber syndrome</td>
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<td>TUMORS</td>
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<td>Cerebral glioma</td>
<td>Many others</td>
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<td>Astrocytoma</td>
<td>OTHER</td>
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<td>Posterior and intraventricular tumors when complicated by hydrocephalus</td>
<td>Retinopathy of prematurity</td>
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<td>Pseudotumor cerebri</td>
<td>Sclerocornea</td>
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<td>Cerebral storage disease</td>
<td>Optic neuritis</td>
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<td>Osteopetrosis</td>
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<td>Other lipidoses and ceroid lipofuscinoses, particularly the late-onset disorders such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt</td>
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<td>Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome</td>
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<td>Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica</td>
<td>Neurofibromatosis</td>
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| covered (occlusion therapy) or blurred with glasses (fogging) or drops (penalization therapy) to stimulate proper visual development of the more severely affected eye. Occlusion therapy may provide a more rapid improvement in vision, but some children may better tolerate atropine penalization. The best treatment for any one patient should be selected on an individual basis. The goals of treatment should be thoroughly understood, and the treatment carefully supervised. Close monitoring of amblyopia therapy by an ophthalmologist is essential, especially in the very young, to avoid deprivation amblyopia in the good eye. Many families need reassurance and support throughout the trying course of treatment. Although full-time occlusion has historically been considered the best way to treat children with amblyopia, a series of prospective studies has shown that some children can achieve similar results with part-time patching or through the use of atropine drops. Historical thought was that older children would not respond to amblyopia therapy; Recent studies now suggest children deemed visually mature who demonstrate amblyopia, particularly refractive or anisometropic in etiology, can demonstrate improvement in vision with appropriate therapy.

DIPLOPIA

Diplopia, or double vision, is generally a result of a misalignment of the visual axes. Occluding either eye relieves the diplopia if it is binocular in origin. Affected children commonly squint, cover 1 eye with a hand, or assume an abnormal head posture (a face turn or head tilt) to alleviate the bothersome sensation. These behaviors, especially in preverbal children, are important clues to diplopia. The onset of diplopia in any child warrants prompt evaluation; it may signal the onset of a serious problem such as increased intracranial pressure, a brain tumor, infection (Lyme disease), migraine, Guillain-Barré syndrome, or an orbital mass.

Monocular diplopia results from dislocation of the lens, cataract, dry eyes, or some defect in the media or macula. With this type of diplopia, occluding the nondiplopic eye will not relieve the symptoms. Monocular diplopia may often have psychological causes.

SUPPRESSION

In the presence of strabismus, diplopia occurs secondary to the same image falling on different regions of the retina in each eye. In a visually
immature child, a process may occur in the cortex that eliminates the
disability of seeing double. This is an active process and is termed sup-
pression. It develops only in children. Although suppression eliminates
the annoying symptom of diplopia, it is the potential awareness of a
second image that tends to keep our eyes properly aligned. Once sup-
pression develops, it may allow an intermittent strabismus to become
constant or strabismus to redevelop later in life, even after successful
treatment during childhood.

AMAUROSIS

Amaurosis is partial or total loss of vision; the term is usually reserved
for profound impairment, blindness, or near blindness. When amaurosis
exists from birth, primary consideration in the differential diagnosis
must be given to developmental malformations, damage consequent
to gestational or perinatal infection, anoxia or hypoxia, perinatal
trauma, and the genetically determined diseases that can affect the eye
itself or the visual pathways. Often, the reason for amaurosis can be
readily determined by objective ophthalmic examination; examples are
severe microphthalmia, corneal opacification, dense cataracts, chorio-
retinal scars, macular defects, retinal dysplasia, and severe optic nerve
hypoplasia. In other cases, an intrinsic retinal disease may not be
apparent on initial ophthalmoscopic examination or the defect may
involve the brain and not the eye. Neuroradiologic (MRI or CT) and
electrophysiologic (electroretinography) evaluation may be especially
helpful in these cases.

Amaurosis that develops in a child who once had useful vision has
different implications. In the absence of obvious ocular disease (cata-
tract, chorioretinitis, retinoblastoma, retinitis pigmentosa), consider-
ation must be given to many neurologic and systemic disorders that
can affect the visual pathways. Amaurosis of rather rapid onset may
indicate an encephalopathy (hypertension), infectious or para-infec-
tious processes, vasculitis, migraine, leukemia, toxins, or trauma. It
may be caused by acute demyelinating disease affecting the optic
nerves, chiasm, or cerebrum. In some cases, precipitous loss of vision
is a result of increased intracranial pressure, rapidly progressive hydro-
cephalus, or dysfunction of a shunt. More slowly progressive visual loss
suggests tumor or neurodegenerative disease. Gliomas of the optic
nerve and chiasm and cranioopharyngiomas are primary diagnostic
considerations in children who show progressive loss of vision.

Clinical manifestations of impairment of vision vary with the age
and abilities of a child, the mode of onset, and the laterality and severity
of the deficit. The first clue to amaurosis in an infant may be nystagmus
or strabismus, with the vision deficit itself passing undetected for
some time. Timidity, clumsiness, or behavioral change may be the
initial clues in the very young. Deterioration in school progress and
indifference to school activities are common signs in an older child.
School-age children often try to hide their disability and, in the case of
very slowly progressive disorders, may not themselves realize the
severity of the problem; some detect and promptly report small changes
in their vision.

Any evidence of loss of vision requires prompt and thorough oph-
thalmic evaluation. Complete delineation of childhood amaurosis and
its cause may require extensive investigation involving neurologic
evaluation, electrophysiologic tests, neuroradiologic procedures, and
sometimes metabolic and genetic studies. Furthermore, attendant
special educational, social, and emotional needs must be met.

NYCTALOPIA

Nyctalopia, or night blindness, is vision that is defective in reduced
illumination. It generally implies impairment in function of the rods,
particularly in dark adaptation time and perceptual threshold. Station-
ary congenital night blindness may occur as an autosomal dominant,
autosomal recessive, or X-linked recessive condition. It may be associ-
ated with myopia and nystagmus. Children may have excessive prob-
lems going to sleep in a dark room, which may be mistaken for a
behavioral problem. Progressive night blindness usually indicates
primary or secondary retinal, choroidal, or vitreoretinal degeneration
(see Chapter 630); it occurs also in vitamin A deficiency or as a result
of retinotoxic drugs such as quinine.

PSYCHOGENIC DISTURBANCES

Vision problems of psychogenic origin are common in school-age
children. Both conversion reactions and willful feigning are encoun-
tered. The usual manifestation is a report of reduced visual acuity in 1
or both eyes. Another common manifestation is constriction of the
visual field. In some cases, the symptom is diplopia or polyopia (see
Chapters 22 and 25).

Important clues to the diagnosis are inappropriate affect, excessive
grimacing, inconsistency in performance, and suggestibility. A thor-
ough ophthalmologic examination is essential to differentiate organic
from functional visual disorders. Affected children usually fare well with reassurance and positive
suggestions. In some cases, psychiatric care is indicated. In all cases,
the approach must be supportive and nonpunitive.

DYSLEXIA

This is the inability to develop the capability to read at an expected
level despite an otherwise normal intellect. The terms reading disability
and dyslexia are often used interchangeably. Most dyslexic individuals
also display poor writing ability. Dyslexia is a primary reading disorder
and should be differentiated from secondary reading difficulties caused
by intellectual disability, environmental or educational deprivation,
and systemic physical or other organic brain or eye diseases. Because
there is no one standard test for dyslexia, the diagnosis is usually made
by comparing reading ability with intelligence and standard reading
expectations. Dyslexia is a language-based disorder and is not caused
by any defect in the eye or visual acuity per se, nor is it attributable to
a defect in ocular motility or binocular alignment. Although ophthal-
mologic evaluation of children with a reading problem is recom-
ended to diagnose and correct any concurrent ocular problems such
as a refractive error, amblyopia, or strabismus, treatment directed to
the eyes themselves cannot be expected to correct developmental dys-
lexia (see Chapter 34).

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

ANIRIDIA

The term aniridia is a misnomer because iris tissue is usually present, although it is hypoplastic (Fig. 622-1). Two thirds of the cases are dominantly transmitted with a high degree of penetrance. The other third of cases are sporadic and are considered to be new mutations. The condition is bilateral in 98% of all patients, regardless of the means of transmission, and is found in approximately 1/50,000 persons. PAX6 is the mutated gene at the chromosome 11p3 region.

Aniridia is a panocular disorder and should not be thought of as an isolated iris defect. Macular and optic nerve hypoplasias are commonly present and lead to decreased vision and sensory nystagmus. The visual acuity is measured as 20/200 in most patients, although the vision may occasionally be better. Other ocular deformities are common and may involve the lens and cornea. The cornea may be small, and a cellular infiltrate (pannus) occasionally develops in the superficial layers of
COLOBOMA OF THE IRIS

This developmental defect may present as a defect in a sector of the iris, a hole in the substance of the iris, or a notch in the pupillary margin (Fig. 622-2). Simple colobomas are frequently transmitted as an autosomal dominant trait. Because of the anatomic location of the embryonic fissure, an iris coloboma is always located inferiorly, giving the iris a keyhole appearance. An iris coloboma may be the only externally visible part of an extensive malclosure of the embryonic fissure that also involves the fundus and optic nerve. When this occurs, vision is likely to be severely affected. Therefore, all children with an iris coloboma should undergo a full ophthalmologic examination.

MICROCORIA

Microcoria (congenital miosis) appears as a small pupil that does not react to light or accommodation and that dilates poorly, if at all, with medication. The condition may be unilateral or bilateral. In bilateral cases, the degree of miosis may be different in each eye. The eye may be otherwise normal or may demonstrate other abnormalities of the anterior segment. Congenital microcoria is usually transmitted as an autosomal dominant trait, although it may occur sporadically.

CONGENITAL MYDRIASIS

In this disorder, the pupils appear dilated, do not constrict significantly to light or near gaze, and respond minimally to miotic agents. The iris is otherwise normal, and affected children are usually healthy. Trauma, pharmacologic mydriasis, and neurologic disorders should be considered. Many apparent cases of congenital mydriasis show abnormalities of the central iris structures and may be considered a form of aniridia.

DYSCORIA AND CORECTOPIA

Dyscoria is abnormal shape of the pupil, and corectopia is abnormal pupillary position. They may occur together or independently as congenital or acquired anomalies.

Congenital corectopia is usually bilateral and symmetric and rarely occurs as an isolated anomaly; it is usually accompanied by dislocation of the lens (ectopia lentis et pupillae), and the lens and pupil are commonly dislocated in opposite directions. Ectopia lentis et pupillae is transmitted as an autosomal recessive disorder; consanguinity is common. It is associated with mutations in ADAMTSL4, a secreted glycoprotein widely distributed in the eye, which binds fibrillin-1 microfibrils and accelerates microfibril biogenesis.

When acquired, distortion and displacement of the pupil are frequently a result of trauma or intraocular inflammation. Prolapse of the iris after perforating injuries of the eye leads to peaking of the pupil in the direction of the perforation. Posterior synechiae (adhesions of the iris to the lens) are commonly seen when inflammation due to any cause occurs in the anterior segment.

ANISOCORIA

This is inequality of the pupils. The difference in size may be a result of local or neurologic disorders. As a rule, if the inequality is more pronounced in the presence of bright focal illumination or on near gaze, there is a defect in pupillary constriction and the larger pupil is abnormal. If the anisocoria is worse in reduced illumination, a defect in dilation exists and the smaller pupil is abnormal. Neurologic causes of anisocoria (parasympathetic or sympathetic lesions) must be differentiated from local causes such as synechiae (adhesions), congenital iris defects (colobomas, aniridia), and pharmacologic effects. Horner syndrome is an important cause of anisocoria (see below). Simple central anisocoria may occur in otherwise healthy individuals.

DILATED FIXED PUPIL

Differential diagnosis of a dilated unreactive pupil includes internal ophthalmoplegia caused by a central or peripheral lesion, Hutchinson pupil of transtentorial herniation, tonic pupil, pharmacologic blockade, and iridoplegia secondary to ocular trauma.

The most common cause of a dilated unreactive pupil is purposeful or accidental instillation of a cycloplegic agent, particularly atropine and related substances. Central nervous system lesions, such as a pinealoma, may cause internal ophthalmoplegia in children. Because the external surface of the oculomotor nerve carries the fibers responsible for pupillary constriction, compression of the nerve along its intracranial course may be associated with internal ophthalmoplegia, even before the development of ptosis or an ocular motility deficit. Although
ophthalmoplegic migraine is a common cause of a 3rd nerve palsy with pupillary involvement in children, an intracranial aneurysm must also be considered in the differential diagnosis. The blown pupil of transtentorial herniation, occurring with increasing intracranial pressure, is generally unilateral, and patients usually are obviously ill. The pilocarpine test can help differentiate neurologic iridoplegia from pharmacologic blockade. In the case of neurologic iridoplegia, the dilated pupil constricts within minutes after instillation of 1 or 2 drops of 0.5–1% pilocarpine; if the pupil has been dilated with atropine, pilocarpine has no effect. Because pilocarpine is a long-acting drug, this test is not to be used in acute situations in which pupillary signs must be carefully monitored. Because of the consensual pupil response to light, even complete uniocular blindness does not cause a unilaterally dilated pupil.

**Tonic Pupil**

This is typically a large pupil that reacts poorly to light (the reaction may be very slow or essentially nil), reacts poorly and slowly to accommodation, and dilates in a slow, tonic manner. The features of tonic pupil are explained by cholinergic supersensitivity of the sphincter after peripheral (postganglionic) denervation and imperfect reinnervation. A distinctive feature of a tonic pupil is its sensitivity to dilute cholinergic agents. Instillation of 0.125% pilocarpine causes significant constriction of the involved pupil and has little or no effect on the unaffected side. The condition is usually unilateral.

Tonic pupil may develop after the acute stage of a partial or complete iridoplegia. It can be seen after trauma to the eye or orbit and may occur in association with toxic or infectious conditions. For those in the pediatric age group, tonic pupil is uncommon. Infectious processes (primarily viral syndromes) and trauma are the primary causes. Features of tonic pupil may also be seen in infants and children with familial dysautonomia (Riley-Day syndrome), although the significance of these findings has been questioned. Tonic pupil has also been reported in young children with Charcot-Marie-Tooth disease. The occurrence of tonic pupil in association with decreased deep tendon reflexes in young women is referred to as Adie syndrome.

**Marcus Gunn Pupil**

This relative afferent pupillary defect indicates an asymmetric, prechiasmatic, afferent conduction defect. It is best demonstrated by the swinging flashlight test, which allows comparison of the direct and consensual pupillary responses in both eyes. With patients fixing on a distant target (to control accommodation), a bright focal light is directed alternately into each eye in turn. In the presence of an afferent lesion, both the direct response to light in the affected eye and the consensual response in the other eye are normal. Swinging the light to the better or normal eye causes both pupils to react (constrict) normally. Swinging the light back to the affected eye causes both pupils to redilate to some degree, reflecting the defective conduction. This is a very sensitive and useful test for detecting and confirming optic nerve and retinal disease. This test is only abnormal if there is a “relative” difference in the conduction properties of the optic nerves. Therefore, patients with bilateral and symmetrical optic nerve disease will not demonstrate an afferent pupillary defect. A subtle relative afferent defect may be found in some children with amblyopia.

**Horner Syndrome**

The principal signs of oculosympathetic paresis (Horner syndrome) are homolateral miosis, mild ptosis, and apparent enophthalmos with slight elevation of the lower lid as a result of the slight ptosis. Patients may also have decreased facial sweating, increased amplitude of accommodation, and transient decrease in intraocular pressure. If paralysis of the ocular sympathetic fibers occurs before the age of 2 yr, heterochromia iridis with hypopigmentation of the iris may occur on the affected side (Fig. 622.3).

Oculosympathetic paralysis may be caused by a lesion (tumor, trauma, infarction) in the midbrain, brainstem, upper spinal cord, neck, middle fossa, or orbit. Congenital oculosympathetic paresis, often as part of Klumpke brachial palsy, is common, although the ocular signs, particularly the anisocoria, may pass undetected for years. Horner syndrome is also seen in some children after thoracic surgery. Congenital Horner syndrome may occur in association with vertebral anomalies and with enterogenous cysts. In some infants and children, Horner syndrome is the presenting sign of tumor in the mediastinal or cervical region, particularly neuroblastoma. Rare causes of Horner syndrome, such as vascular lesions, also occur in the pediatric age group. In many cases, no cause of congenital Horner syndrome can be identified. Occasionally, the condition is familial. When the cause of Horner syndrome is in question, investigative procedures should be implemented and may include imaging of the head, neck, and chest as well as 24-hr urinary catecholamine assay. Examining old photographs and old records can sometimes be helpful in establishing the age at onset of Horner syndrome.

The cocaine test is useful in diagnosing oculosympathetic paralysis; a normal pupil dilates within 20–45 min after instillation of 1 or 2 drops of 4% cocaine, whereas the miotic pupil of an oculosympathetic paresis dilates poorly, if at all, with cocaine. In some cases, there is denervation supersensitivity to dilute phenylephrine; 1 or 2 drops of a 1% solution dilates the affected pupil but not the normal one. Furthermore, instillation of 1% hydroxyamphetamine hydrobromide dilates the pupil only if the postganglionic sympathetic neuron is intact.

**Paradoxical Pupil Reaction**

Some children exhibit paradoxical constriction of the pupils to darkness. An initial brisk constriction of the pupils occurs when the light is turned off, followed by slow redilation of the pupils. The response to direct light stimulation and the near response are normal. The mechanism is not clear, but paradoxical constriction of the pupils in reduced light can be a sign of retinal or optic nerve abnormalities. The phenomenon has been observed in children with congenital stationary night blindness, albinism, retinitis pigmentosa, Leber congenital retinal amaurosis, and Best disease. It has also been observed in those with optic nerve anomalies, optic neuritis, optic atrophy, and possibly amblyopia. Thus, children with paradoxical pupillary constriction to darkness should have a thorough ophthalmologic examination.

**Persistent Pupillary Membrane**

Involution of the pupillary membrane and anterior vascular capsule of the lens is usually completed during the 5th–6th mo of fetal development. It is common to see some remnants of the pupillary membrane in newborns, particularly in premature infants. These membranes are...
nonpigmented strands of obliterated vessels that cross the pupil and may secondarily attach to the lens or cornea. The remnants tend to atrophy in time and usually present no problem. In some cases, however, significant remnants that remain obscure the pupil and interfere with vision. Rarely, there is patency of the vascular elements; hyphema may result from rupture of persistent vessels.

Intervention must be considered to minimize amblyopia in infants with extensive persistent pupillary membrane of sufficient degree to interfere with vision in the early months of life. In some cases, mydriatics and occlusion therapy may be effective, but in others, surgery may be needed to provide an adequate pupillary aperture.

**HETEROCHROMIA**

In heterochromia, the 2 irides are of different color (heterochromia iridium) or a portion of an iris differs in color from the remainder (heterochromia iridis). Simple heterochromia may occur as an autosomal dominant characteristic. Congenital heterochromia is also a feature of Waardenburg syndrome, an autosomal dominant condition characterized principally by lateral displacement of the inner canthi and puncta, pigmented disturbances (usually a median white forelock and patches of hypopigmentation of the skin), and defective hearing. Change in the color of the iris may occur as a result of trauma, hemorrhage, intraocular inflammation (iritis, uveitis), intraocular tumor (especially retinoblastoma), intraocular foreign body, glaucoma, iris atrophy, oculosympathetic palsy (Horner syndrome), melanosis oculi, previous intraocular surgery, and some glaucoma medications.

**OTHER IRIS LESIONS**

Discrete nodules of the iris, referred to as *Lisch nodules*, are commonly seen in patients with neurofibromatosis (see Chapter 596.1). Lisch nodules represent melanocytic hamartomas of the iris and vary from slightly elevated pigmented areas to distinct ball-like excrencences. The nodules cause no visual disturbance. Lisch nodules are found in 92-100% of individuals older than 5 yr of age who have neurofibromatosis. Slit-lamp identification of these nodules may help to fulfill the criteria required to confirm the diagnosis of neurofibromatosis.

In leukemia (see Chapter 495), there may be infiltration of the iris, sometimes with *hypopyon*, an accumulation of white blood cells in the anterior chamber, which may herald relapse or involvement of the central nervous system.

The lesion of *juvenile xanthogranuloma* (nevoxanthoendothelioma; see Chapter 670) may occur in the eye as a yellowish fleshy mass or plaque of the iris. Spontaneous hyphema (blood in the anterior chamber), glaucoma, or a red eye with signs of uveitis may be associated. A search for the skin lesions of xanthogranuloma should be made in any infant or young child with spontaneous hyphema. In many cases, the ocular lesion responds to topical corticosteroid therapy.

**LEUKOCORIA**

This includes any white pupillary reflex, or so-called cat’s-eye reflex. Primary diagnostic considerations in any child with leukocoria are cataract, persistent hyperplastic primary vitreous, cicatricial retinopathy of prematurity, retinal detachment and retinoschisis, larval granulomatosis, and retinoblastoma (Fig. 622-4). Also to be considered are endophthalmitis, organized vitreous hemorrhage, leukemic ophthalmopathy, exudative retinopathy (as in Coats disease), and less-common conditions such as medulloepithelioma, massive retinal gliosis, the retinal pseudotumor of Norrie disease, the so-called pseudoglioma of the Bloch-Sulzberger syndrome, retinal dysplasia, and the retinal lesions of the phakomatoses. A white reflex may also be seen with fundus coloboma, large atrophic chorioretinal scars, and ectopic mullation of retinal nerve fibers. Leukocoria is an indication for prompt and thorough evaluation.

The diagnosis can often be made by direct examination of the eye by ophthalmoscopy and biomicroscopy. Ultrasonographic and radiologic examinations are often helpful. In some cases, the final diagnosis rests with a pathologist.

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Chapter 623
Disorders of Eye
Movement and Alignment

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STRABISMUS
Strabismus, or misalignment of the eyes, is one of the most common eye problems encountered in children, affecting approximately 4% of children younger than 6 yr of age. Strabismus can result in vision loss (amblyopia) and can have significant psychological effects. Early detection and treatment of strabismus are essential to prevent permanent visual impairment. Of children with strabismus, 30-50% develop amblyopia. Restoration of proper alignment of the visual axis must occur at an early stage of visual development to allow these children a chance to develop normal binocular vision. The word strabismus means "to squint or to look obliquely." Many terms are used in discussing and characterizing strabismus.

Orthophoria is the ideal condition of exact ocular balance. It implies that the oculomotor apparatus is in perfect equilibrium so that the eyes remain coordinated and aligned in all positions of gaze and at all distances. Even when binocular vision is interrupted, as by occlusion of one eye, truly orthophoric individuals maintain perfect alignment. Orthophoria is seldom encountered because the majority of individuals have a small latent deviation (heterophoria).

Heterophoria is a latent tendency for the eyes to deviate. This latent deviation is normally controlled by fusional mechanisms that provide binocular vision or avoid diplopia (double vision). The eye deviates only under certain conditions, such as fatigue, illness, or stress, or during tests that interfere with maintenance of these normal fusional abilities (such as covering one eye). If the amount of heterophoria is large, it may give rise to bothersome symptoms, such as transient diplopia (double vision), headaches, or asthenopia (eyestrain). Some degree of heterophoria is found in normal individuals; it is usually asymptomatic.

Heterotropia is a misalignment of the eyes that is constant. It occurs because of an inability of the fusional mechanism to control the deviation. Tropias can be alternating, involving both eyes, or unilateral. In an alternating tropia, there is no preference for fixation of either eye, and both eyes drift with equal frequency. Because each eye is used periodically, vision usually develops normally. A unilateral tropia is a more serious situation because only 1 eye is constantly misaligned. The undeviated eye becomes the preferred eye, resulting in loss of vision or amblyopia of the deviated eye.
 Disorders of gaze. Deviation is constant, or relatively constant, in the various directions. Comitant strabismus is the most common type of strabismus. The etiologic classification of strabismus is complex, and the causative forms of strabismus must be distinguished; there are comitant and noncomitant types.

Diagnosis

Many techniques are used to assess ocular alignment and movement of the eyes to aid in diagnosing strabismic disorders. In a child with strabismus or any other ocular disorder, assessment of visual acuity is mandatory. Decreased vision in 1 eye requires evaluation for a strabismus or other ocular abnormalities, which may be difficult to discern on a brief screening evaluation. Even strabismic deviations of only a few degrees in magnitude, too small to be evident by gross inspection, may lead to amblyopia and significant vision loss.

Corneal light reflex tests are perhaps the most rapid and easily performed diagnostic tests for strabismus. They are particularly useful in children who are uncooperative and in those who have poor ocular fixation. To perform the Hirschberg corneal reflex test, the examiner projects a light source onto the cornea of both eyes simultaneously as a child looks directly at the light. Comparison should then be made of the placement of the corneal light reflex in each eye. In straight eyes, the light reflection appears symmetric and, because of the relationship between the cornea and the macula, slightly nasal to the center of each pupil. If strabismus is present, the reflected light is asymmetric and appears displaced in one eye. The Krimsky method of the corneal reflex test uses prisms placed over one or both eyes to align the light reflections. The amount of prism needed to align the reflections is used to measure the degree of deviation. Although it is a useful screening test, corneal light reflex testing may not detect a small angle or an intermittent strabismus.

Cover tests for strabismus require a child’s attention and cooperation, good eye movement capability, and reasonably good vision in each eye. If any of these are lacking, the results of these tests may not be valid. These tests consist of the cover–uncover test and the alternate cover test. In the cover–uncover test, a child looks at an object in the distance, preferably 6 m away. An eye chart is commonly used for fixation in children older than 3 yr of age. For younger children, a noise-making toy or movie helps hold their attention for the test. As the child looks at the distant object, the examiner covers 1 eye and watches for movement of the uncovered eye. If no movement occurs, there is no apparent misalignment of that eye. After 1 eye is tested, the same procedure is repeated on the other eye. When performing the alternate cover test, the examiner rapidly covers and uncovers each eye, shifting back and forth from one eye to the other. If the child has an ocular deviation, the eye rapidly moves as the cover is shifted to the other eye. Both the cover–uncover test and the alternate cover test should be performed at both distance and near fixation. The cover–uncover test differentiates tropias, or manifest deviations, from latent deviations, called phorias.

Clinical Manifestations and Treatment

The etiologic classification of strabismus is complex, and the causative types must be distinguished; there are comitant and noncomitant forms of strabismus.

Comitant Strabismus

Comitant strabismus is the most common type of strabismus. The individual extraocular muscles usually have no defect. The amount of deviation is constant, or relatively constant, in the various directions of gaze.

Pseudostrabismus (pseudoesotropia) is one of the most common reasons a pediatric ophthalmologist is asked to evaluate an infant. This condition is characterized by the false appearance of strabismus when the visual axes are aligned accurately. This appearance may be caused by a flat, broad nasal bridge, prominent epicanthal folds, or a narrow interpupillary distance. The observer may see less white sclera nasally than would be expected, and the impression is that the eye is turned in toward the nose, especially when the child gazes to either side. Parents frequently comment that when their child looks to the side, the eye almost disappears from view. Pseudoesotropia can be differentiated from a true misalignment of the eyes when the corneal light reflex is centered in both eyes and when the cover–uncover test shows no relfixation movement. Once pseudoesotropia has been confirmed, parents can be reassured that the child will outgrow the appearance of esotropia. As the child grows, the bridge of the nose becomes more prominent and displaces the epicanthal folds, and the medial sclera becomes proportional to the amount visible on the lateral aspect. It is the appearance of crossing that the child will outgrow. Some parents of children with pseudoesotropia erroneously believe that their child has an actual esotropia that will resolve on its own. Because true esotropia can develop later in children with pseudoesotropia, parents and pediatricians should be cautioned that reassessment is required if the apparent deviation does not improve.

Esodeviations are the most common type of ocular misalignment in children and represent >50% of all ocular deviations. Congenital esotropia is a confusing term. Few children who are diagnosed with this disorder are actually born with an esotropia. Most reports in the literature have, therefore, considered infants with confirmed onset earlier than 6 mo as having the same condition, which some observers have designated infantile esotropia.

Between 2 and 4 mo of age, many infants have infantile esotropia (neonatal misalignments), which in most resolve spontaneously. Those that resolve without treatment do so before 10–12 wk of age and had intermittent or variable deviations, while those who may benefit from active treatment have persistent esotropia (10 weeks–6 mo of age), a constant esotropia (40 PD), a refractive error ≤ +3.00 D, and the absence of prematurity, developmental delay, meningitis, myasthenia, eye anomalies, and incomitant or paralytic strabismus. The evaluation is noted in Figure 623-1.

The characteristic angle of congenital esodeviations is large and constant (Fig. 623-2). Because of the large deviation, cross-fixation is frequently encountered. This is a condition in which the child looks to the right with the left eye and to the left with the right eye. With cross-fixation, there is no need for the eye to turn away from the nose (abduction) as the adducting eye is used in side gaze; this condition simulates a 6th nerve palsy. Abduction can be demonstrated by the doll’s-head maneuver or by patching 1 eye for a short time. Children with congenital esotropia tend to have refractive errors similar to those of normal children of the same age. This contrasts with the characteristic high level of farsightedness associated with accommodative esotropia. Amblyopia is common in children with congenital esotropia.

The primary goal of treatment in congenital esotropia is to eliminate or reduce the deviation as much as possible. Ideally, this results in normal sight in each eye, in straight-looking eyes, and in the development of binocular vision. Early treatment is more likely to lead to the development of binocular vision, which helps to maintain long-term ocular alignment. Once any associated amblyopia is treated, surgery is performed to align the eyes. Even with successful surgical alignment, it is common for vertical deviations to develop in children with a history of congenital esotropia. The 2 most common forms of vertical deviations to develop are inferior oblique muscle overaction and dissociated vertical deviation. In inferior oblique muscle overaction, the overactive inferior oblique muscle produces an upshoot of the eye closest to the nose when the patient looks to the side (Fig. 623-3). In dissociated vertical deviation, 1 eye drifts up slowly with no movement of the other eye. Surgery may be necessary to treat either or both of these conditions.

It is important that parents realize that early successful surgical alignment is only the beginning of the treatment process. Because many children may redevelop strabismus or amblyopia, they need to be monitored closely during the visually immature period of life.
Accommodative esotropia is defined as a "convergent deviation of the eyes associated with activation of the accommodative (focusing) reflex." It usually occurs in a child who is between 2 and 3 yr of age and who has a history of acquired intermittent or constant crossing. Amblyopia occurs in the majority of cases.

The mechanism of accommodative esotropia involves uncorrected hyperopia, accommodation, and accommodative convergence. The image entering a hyperopic (farsighted) eye is blurred. If the amount of hyperopia is not significant, the blurred image can be sharpened by accommodating (focusing of the lens of the eye). Accommodation is closely linked with convergence (eyes turning inward). If a child's hyperopic refractive error is large or if the amount of convergence that occurs in response to each unit of accommodative effort is great, esotropia may develop.

Figure 623-1 Work-up of infant ≥4 mo of age with esotropia. CP, cerebral palsy; DS, Down syndrome; PVL, periventricular leukomalacia. (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 74.4, p. 767.)

Figure 623-2 Congenital esotropia. Note the large angle of crossing.

Figure 623-3 Inferior oblique muscle overaction.
To treat accommodative esotropia, the full hyperopic (farsighted) correction is initially prescribed. These glasses eliminate a child’s need to accommodate and therefore correct the esotropia (Fig. 623-4). Although many parents are initially concerned that their child will not want to wear glasses, the benefits of binocular vision and the decrease in the focusing effort required to see clearly provide a strong stimulus to wear glasses, and they are generally accepted well. The full hyperopic correction sometimes straightens the eye position at distance fixation but leaves a residual deviation at near fixation; this may be observed or treated with bifocal lenses or surgery.

It is important to warn parents of children with accommodative esotropia that the esodeviation may appear to increase without glasses after the initial correction is worn. Parents frequently state that before wearing glasses, their child had a small esodeviation, whereas after removal of the glasses, the esodeviation becomes quite large. Parents often blame the increased esodeviation on the glasses. This apparent increase is a result of a child’s using the appropriate amount of accommodative effort after the glasses have been worn. When these children remove their glasses, they continue to use an accommodative effort to bring objects into proper focus and increase the esodeviation.

Most children maintain straight eyes once initially treated. Because hyperopia generally decreases with age, patients may outgrow the need to wear glasses to maintain alignment. In some patients, a residual esodeviation persists even when wearing their glasses. This condition commonly occurs when there is a delay between the onset of accommodative esotropia and treatment. In others, the esotropia may initially be eliminated with glasses but crossing redevelops and is not correctable with glasses. The crossing that is no longer correctable with glasses is the deteriorated or nonaccommodative portion. Surgery for this portion of the crossing may be indicated to restore binocular vision.

Exodeviations are the second most common type of misalignment.

The divergent deviation may be intermittent or constant. Intermittent exotropia is the most common exodeviation in childhood. It is characterized by outward drifting of 1 eye, which usually occurs when a child is fixating at distance. The deviation is generally more frequent with fatigue or illness. Exposure to bright light may cause reflex closure of the exotropic eye. Because the eyes initially can be kept straight most of the time, visual acuity tends to be good in both eyes and binocular vision is initially normal.

Figure 623-4 Accommodative esotropia. Control of deviation with corrective lenses.
6th Nerve Palsy

These palsies produce markedly crossed eyes with limited ability to move the affected eye laterally. Children frequently present with their head turned toward the palsied muscle, a position that helps preserve binocular vision. The esotropia is largest when the eye is moved toward the affected muscle.

Congenital 6th nerve palsies are rare. Decreased lateral gaze in infants is often associated with other disorders, such as congenital esotropia or Duane retraction syndrome. In neonates, a transient 6th nerve paresis can occur; it usually clears spontaneously by 6 wk. It is believed that increased intracranial pressure associated with labor and delivery is the contributing factor.

Acquired 6th nerve palsies in childhood are often an ominous sign because the 6th nerve is susceptible to increased intracranial pressure associated with hydrocephalus and intracranial tumors. Other causes of 6th nerve defects in children include trauma, vascular malformations, meningitis, and Gradenigo syndrome. A benign 6th nerve palsy, which is painless and acquired, can be noted in infants and older children. This is frequently preceded by a febrile illness or upper respiratory tract infection and may be recurrent. Complete resolution of the palsy is usual. Although not uncommon, other causes of an acute 6th nerve palsy should be eliminated before this diagnosis is made.

Strabismus Syndromes

Special types of strabismus have unusual clinical features. Most of these disorders are caused by structural anomalies of the extraocular muscles or adjacent tissues. Most strabismus syndromes produce noncomitant misalignments.

Monocular Elevation Deficiency

A monocular elevation deficit in both abduction and adduction is referred to as monocular elevation deficiency (previously called double-elevator palsy). It may represent a paresis of both elevators, the superior rectus and inferior oblique muscles, or a possible restriction to elevation from a fibrotic inferior rectus muscle. When an affected child fixates with the nonparetic eye, the paretic eye is hypotropia and the ipsilateral upper eyelid may appear ptotic. Fixation with the paretic eye causes a hypertropia of the nonparetic eye and a disappearance of the ptosis (Fig. 623-5). Because the apparent ptosis is actually secondary to the strabismus, correction of the hypertropia treats the pseudoptosis.

Duane Syndrome

This congenital disorder of ocular motility is characterized by retraction of the globe on adduction. This is attributed to the absence of the 6th nerve nucleus and anomalous innervation of the lateral rectus muscle, which results in cocontraction of the medial and lateral rectus muscles on attempted adduction of the affected eye. Within the spectrum of Duane syndrome, patients may exhibit impairment of abduction, impairment of adduction, or upshoot or downshoot of the involved eye on adduction. They may have esotropia, exotropia, or relatively straight eyes. Many exhibit a compensatory head posture to maintain single vision. Some develop amblyopia. Surgery to improve alignment or to reduce a noticeable face turn can be helpful in selected cases. Duane syndrome usually occurs sporadically. It is sometimes inherited as an autosomal dominant trait. It usually occurs as an isolated condition but may occur in association with various other ocular and systemic anomalies.

Möbius Syndrome

The distinctive features of Möbius syndrome are congenital facial paresis and abduction weakness. The facial palsy is commonly bilateral, frequently asymmetric, and often incomplete, tending to spare the lower face and platysma. Ectropion, epiphora, and exposure keratopathy may develop. The abduction defect may be unilateral or bilateral. Esotropia is common. The cause is unknown. Whether the primary defect is maldevelopment of cranial nerve nuclei, hypoplasia of the muscles, or a combination of central and peripheral factors is unclear. Some familial cases have been reported. Associated developmental defects may include ptosis, palatal and lingual palsy, hearing loss, pectoral and lingual muscle defects, micrognathia, syndactyly, supernumerary digits, and the absence of hands, feet, fingers, or toes. Surgical correction of the esotropia is indicated and any attendant amblyopia should be treated.

Brown Syndrome

In this syndrome, elevation of the eye in the adducted position is restricted (Fig. 623-6). An associated downward deviation of the affected eye in adduction may also occur. A compensatory head posture may be evident. Brown syndrome occurs as a result of restriction of the superior oblique tendon as it moves through the trochlea. Cases may be congenital or acquired. Acquired Brown syndrome may follow trauma to the orbit involving the region of the trochlea or sinus surgery. It may also occur with inflammatory processes, particularly sinusitis and juvenile idiopathic arthritis.

Acquired inflammatory Brown syndrome may respond to treatment with either nonsteroidal medications or corticosteroids. Surgery may be helpful for selected cases of Brown syndrome.

Parinaud Syndrome

This eponym designates a palsy of vertical gaze, isolated or associated with pupillary or nuclear oculomotor (3rd cranial nerve) paresis. It indicates a lesion affecting the mesencephalic tegmentum. The ophthalmic signs of midbrain disease include vertical gaze palsy, dissociation of the pupillary responses to light and to near focus, general pupillomotor paralysis, corectopia, dyscoria, accommodative disturbances, pathologic lid retraction, ptosis, extraocular muscle paresis, and convergence paralysis. Some cases have associated spasms of convergence, convergent retraction nystagmus, and vertical nystagmus, particularly on attempted vertical gaze. Combinations of these signs are referred to as the sylvian aqueduct syndrome.
A principal cause of vertical gaze palsy and associated mesencephalic signs in children is tumor of the pineal gland or third ventricle. Differential diagnosis includes trauma and demyelinating disease. In children with hydrocephalus, impairment of vertical gaze and pathologic lid retraction are referred to as the setting-sun sign. A transient supranuclear disorder of gaze is sometimes seen in healthy neonates.

**CONGENITAL OCULAR MOTOR APRAXIA**

This congenital disorder of conjugate gaze is characterized by a defect in voluntary horizontal gaze; compensatory jerk movement of the head, and retention of slow pursuit and reflexive eye movements. Additional features are absence of the fast (recovery) phase of optokinetic nystagmus and obligate contraversive deviation of the eyes on rotation of the body. Affected children typically are unable to look quickly to either side voluntarily in response to a command or in response to an eccentrically presented object but may be able to follow a slowly moving target to either side. To compensate for the defect in purposive lateral eye movements, children jerk their head to bring the eyes into the desired position and may also blink repetitively in an attempt to change fixation. The signs tend to become less conspicuous with age.

The pathogenesis of congenital ocular motor apraxia is unknown. It may be a result of delayed myelination of the ocular motor pathways. Structural abnormalities of the central nervous system have been found in a few patients, including agenesis of the corpus callosum and cerebellar vermis, porencephaly, hamartoma of the foramen of Monro, and macrocephaly. Many children with congenital ocular motor apraxia show delayed motor and cognitive development.

**NYSTAGMUS**

Nystagmus (rhythmic oscillations of 1 or both eyes) may be caused by an abnormality in any one of the 3 basic mechanisms that regulate position and movement of the eyes: the fixation, conjugate gaze, or vestibular mechanism. In addition, physiologic nystagmus may be elicited by appropriate stimuli (Table 623-1).

**Congenital sensory nystagmus** is generally associated with ocular abnormalities that lead to decreased visual acuity; common disorders that lead to early-onset nystagmus include albinism, aniridia, achromatopsia, congenital cataracts, congenital macular lesions, and congenital optic atrophy. In some instances, nystagmus occurs as a dominant or X-linked characteristic without obvious ocular abnormalities.

**Congenital idiopathic motor nystagmus** is characterized by horizontal jerk oscillations with gaze preponderance; the nystagmus is coarser in one direction of gaze than in the other, with the jerk toward the direction of gaze. There are no ocular anatomic defects that cause the nystagmus, and the visual acuity is generally near normal. There may be a null point in which the nystagmus lessens and the vision improves; a compensatory head posture will develop that places the eyes into the position of least nystagmus. The cause of congenital idiopathic motor nystagmus is unknown; in some instances, it is familial. Eye muscle surgery may be performed to eliminate an abnormal head posture by bringing the point of best vision into straight-ahead gaze.

**Acquired nystagmus** requires prompt and thorough evaluation. Worrisome pathologic types are the gaze-paretic or gaze-evoked oscillations of cerebellar, brainstem, or cerebral disease.

**Nystagmus retractorius** or **convergent nystagmus** is repetitive jerking of the eyes into the orbit or toward each other. It is usually seen with vertical gaze palsy as a feature of Parinaud (sylvian aqueduct) syndrome. The causal condition may be neoplastic, vascular, or inflammatory. In children, nystagmus retractorius suggests particularly the presence of pinealoma or hydrocephalus.

A diagnostic approach to nystagmus is noted in Figures 623-7 and 623-8.

**Spasmus nutans** is a special type of acquired nystagmus in childhood (see also Chapter 597). In its complete form, it is characterized by the triad of pendular nystagmus, head nodding, and torticollis. The nystagmus is characteristically very fine, very rapid, horizontal, and pendular; it is often asymmetric, sometimes unilateral. Signs usually develop within the 1st yr or 2 of life. Components of the triad may develop at various times. In many cases, the condition is benign and self-limited, usually lasting a few months, sometimes years. The cause of this classic type of spasmus nutans, which usually resolves spontaneously, is unknown. Some children exhibiting signs resembling those of spasmus nutans have underlying brain tumors, particularly hypothalamic and chiasmal optic gliomas. Appropriate neurologic and neuro-radiologic evaluation and careful monitoring of infants and children with nystagmus are therefore recommended.

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**Table 623-1: Specific Patterns of Nystagmus**

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>DESCRIPTION</th>
<th>ASSOCIATED CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent nystagmus</td>
<td>Conjugate jerk nystagmus toward viewing eye</td>
<td>Congenital vision defects, occurs with occlusion of eye</td>
</tr>
<tr>
<td>Manifest latent nystagmus</td>
<td>Fast jerk to viewing eye</td>
<td>Strabismus, congenital idiopathic nystagmus</td>
</tr>
<tr>
<td>Periodic alternating</td>
<td>Cycles of horizontal or horizontal-rotary that change direction</td>
<td>Caused by both visual and neurologic conditions</td>
</tr>
<tr>
<td>Seesaw nystagmus</td>
<td>One eye rises and intorts as other eye falls and extorts</td>
<td>Usually associated with optic chiasmal defects</td>
</tr>
<tr>
<td>Nystagmus retractorius</td>
<td>Eyes jerk back into orbit or toward each other</td>
<td>Caused by pressure on mesencephalic tegmentum (Parinaud syndrome)</td>
</tr>
<tr>
<td>Gaze-evoked nystagmus</td>
<td>Jerk nystagmus in direction of gaze</td>
<td>Caused by medications, brainstem lesion, or labyrinthine dysfunction</td>
</tr>
<tr>
<td>Gaze-paretic nystagmus</td>
<td>Eyes jerk back to maintain eccentric gaze</td>
<td>Cerebellar disease</td>
</tr>
<tr>
<td>Downbeat nystagmus</td>
<td>Fast phase beating downward</td>
<td>Posterior fossa disease, drugs</td>
</tr>
<tr>
<td>Upbeat nystagmus</td>
<td>Fast phase beating upward</td>
<td>Brainstem and cerebellar disease; some visual conditions</td>
</tr>
<tr>
<td>Vestibular nystagmus</td>
<td>Horizontal-torsional or horizontal jerks</td>
<td>Vestibular system dysfunction</td>
</tr>
<tr>
<td>Asymmetric or monocular nystagmus</td>
<td>Pendular vertical nystagmus</td>
<td>Disease of retina and visual pathways</td>
</tr>
<tr>
<td>Spasmus nutans</td>
<td>Fine, rapid, pendular nystagmus</td>
<td>Torticollis, head nodding; idiopathic or gliomas of visual pathways</td>
</tr>
</tbody>
</table>

Figure 623-7 Algorithm for the work-up of an infant with nystagmus. ⊘, positive; ⊝, negative; CSNB, congenital stationary night blindness; ERG, electroretinogram; NFL, nerve fiber layer; PHPV, persistent hyperplastic primary vitreous; ROP, retinopathy of prematurity. (From Nelson LB: Harley’s pediatric ophthalmology, ed 4, Philadelphia, 1998, WB Saunders, p. 470.)

Figure 623-8 Classification of nystagmus based on associated diseases. (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 89.2, p. 910.)
OTHER ABNORMAL EYE MOVEMENTS

To be differentiated from true nystagmus are certain special types of abnormal eye movements, particularly opsoclonus, ocular dysmetria, and flutter (Table 623-2).

**Opsoclonus**

Opsoclonus and ataxic conjugate movements are spontaneous, non-rhythmic, multidirectional, chaotic movements of the eyes. The eyes appear to be in agitation, with bursts of conjugate movement of varying amplitude in varying directions. Opsoclonus is most often associated with infectious or autoimmune encephalitis. It may be the first sign of neuroblastoma or other tumors producing a paraneoplastic syndrome.

**Ocular Motor Dysmetria**

This is analogous to dysmetria of the limbs. Affected individuals show a lack of precision in performing movements of refixation, characterized by an overshoot (or undershoot) of the eyes with several corrective to-and-fro oscillations on looking from one point to another. Ocular motor dysmetria is a sign of cerebellar or cerebellar pathway disease.

**Flutter-Like Oscillations**

These intermittent to-and-fro horizontal oscillations of the eyes may occur spontaneously or on change of fixation. They are characteristic of cerebellar disease.

Bibliography is available at Expert Consult.

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>DESCRIPTION</th>
<th>ASSOCIATED CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsoclonus</td>
<td>Multidirectional conjugate movements of varying rate and amplitude</td>
<td>Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome</td>
</tr>
<tr>
<td>Ocular dysmetria</td>
<td>Overshoot of eyes on rapid fixation</td>
<td>Cerebellar dysfunction</td>
</tr>
<tr>
<td>Ocular flutter</td>
<td>Horizontal oscillations with forward gaze and sometimes with blinking</td>
<td>Cerebellar disease, hydrocephalus, or central nervous system neoplasm</td>
</tr>
<tr>
<td>Ocular bobbing</td>
<td>Downward jerk from primary gaze, remains for a few sec, then drifts back</td>
<td>Pontine disease</td>
</tr>
<tr>
<td>Ocular myoclonus</td>
<td>Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement</td>
<td>Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus</td>
</tr>
</tbody>
</table>

Bibliography


Chapter 624
Abnormalities of the Lids
Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

PTOSIS
In blepharoptosis, the upper eyelid droops below its normal level. Congenital ptosis is usually a result of a localized dystrophy of the levator muscle in which the striated muscle fibers are replaced with fibrous tissue. The condition may be unilateral or bilateral and can be familial, transmitted as a dominant trait.

Parents often comment that the eye looks smaller because of the drooping eyelid. The lid crease is decreased or absent where the levator muscle would normally insert below the skin surface. Because the levator is replaced by fibrous tissue, the lid does not move downward fully in downgaze (lid lag). If the ptosis is severe, affected children often attempt to raise the lid by lifting their brow or adapting a chin-up head posture to maintain binocular vision. **Marcus Gunn jaw-winking ptosis** accounts for 5% of ptoses in children. In this syndrome, an abnormal synkinesis exists between the 5th and 3rd cranial nerves; this causes the eyelid to elevate with movement of the jaw. The wink is produced by chewing or sucking and may be more noticeable than the ptosis itself.

Although ptosis in children is often an isolated finding, it may occur in association with other ocular or systemic disorders. Systemic disorders include myasthenia gravis, muscular dystrophy, and botulism. Ocular disorders include mechanical ptosis secondary to lid tumors, blepharophimosis syndrome, congenital fibrosis syndrome, combined levator/superior rectus maldevelopment, and congenital or acquired 3rd nerve palsy. A small degree of ptosis is seen in Horner syndrome (see Chapter 622). A complete ophthalmic and systemic examination is therefore important in the evaluation of a child with ptosis.

**Amblyopia** may occur in children with ptosis. The amblyopia may be secondary to the lid's covering the visual axis (deprivation) or induced astigmatism (anisometropia). When amblyopia occurs, it should generally be treated before treating the ptosis.

**Treatment** of ptosis in a child is indicated for elimination of an abnormal head posture, improvement in the visual field, prevention of amblyopia, and restoration of a normal eyelid appearance. The timing of surgery depends on the degree of ptosis, its cosmetic and functional severity, the presence or absence of compensatory posturing, the wishes of the parents, and the discretion of the surgeon. Surgical treatment is determined by the amount of levator function that is present. A levator resection may be used in children with moderate to good function. In patients with poor or absent function, a frontalis suspension procedure may be necessary. This technique requires that a suspension material be placed between the frontalis muscle and the tarsus of the eyelid. It allows patients to use their brow and frontalis muscle more effectively to raise their eyelid. Amblyopia remains a concern even after surgical correction and should be monitored closely.

EPICANTHAL FOLDS
These vertical or oblique folds of skin extend on either side of the bridge of the nose from the brow or lid area, covering the inner canthal region. They are present to some degree in most young children and become less apparent with age. The folds may be sufficiently broad to cover the medial aspect of the eye, making the eyes appear crossed (pseudoesotropia). Epicanthal folds are a common feature of many syndromes, including chromosomal aberrations (trisomies) and disorders of single genes.

LAGOPHTHALMOS
This is a condition in which complete closure of the lids over the globe is difficult or impossible. It may be paralytic because of a facial palsy...
involving the orbicularis muscle, or spastic, as in thyrotoxicosis. It may be structural when retraction or shortening of the lids results from scarring or atrophy consequent to injury (burns) or disease. For example, children with various craniosynostosis syndromes can have problematic lagophthalmos. Infants with collodion membrane may have temporary lagophthalmos caused by the restrictive effect of the membrane on the lids. Lagophthalmos may accompany proptosis or buphthalmos (enlarged cornea because of elevated intraocular pressure) when the lids, although normal, cannot effectively cover the enlarged or protuberant eye. A degree of physiologic lagophthalmos may occur normally during sleep, but functional lagophthalmos in an unconscious or debilitated patient can be a problem.

In patients with lagophthalmos, exposure of the eye may lead to drying, infection, corneal ulceration, or perforation of the cornea; the result may be loss of vision, even loss of the eye. In lagophthalmos, protection of the eye by artificial tear preparations, opthalmic ointment, or moisture chambers is essential. Gauze pads are to be avoided because the gauze may abrade the cornea. In some cases, surgical closure of the lids (tarsorrhaphy) may be necessary for long-term protection of the eye.

**LID RETRACTIONS**

Pathologic retraction of the lid may be myogenic or neurogenic. Myogenic retraction of the upper lid occurs in thyrotoxicosis, in which it is associated with 3 classic signs: a staring appearance (Dalrymple sign), infrequent blinking (Stellwag sign), and lag of the upper lid on downward gaze (von Graefe sign).

Neurogenic retraction of the lids may occur in conditions affecting the anterior mesencephalon. Lid retraction is a feature of the syndrome of the sylvian aqueduct. In children, it is commonly a sign of hydrocephalus. It may occur with meningitis. Paradoxical retraction of the lid is seen in the Marcus Gunn jaw-winking syndrome. It may also be seen with attempted eye movement after recovery from a 3rd nerve palsy, if aberrant regeneration of the oculomotor nerve fibers has occurred.

Simple staring and the physiologic or reflexive lid retraction (“eye popping”), in contrast to pathologic lid retractions, occur in infants in response to a sudden reduction in illumination or as a startle reaction.

**ECTROPION, ENTROPION, AND EPIBLEPHARON**

Ectropion is eversion of the lid margin; it may lead to overflow of tears (epiphora) and subsequent maceration of the skin of the lid, inflammation of exposed conjunctiva, or superficial exposure keratopathy. Common causes are scarring consequent to inflammation, burns, or trauma and weakness of the orbicularis muscle as a result of facial weakness or atrophy consequent to injury (burns) or disease. For example, children with various craniosynostosis syndromes can have problematic lagophthalmos. Infants with collodion membrane may have temporary lagophthalmos caused by the restrictive effect of the membrane on the lids. Lagophthalmos may accompany proptosis or buphthalmos (enlarged cornea because of elevated intraocular pressure) when the lids, although normal, cannot effectively cover the enlarged or protuberant eye. A degree of physiologic lagophthalmos may occur normally during sleep, but functional lagophthalmos in an unconscious or debilitated patient can be a problem.

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**BLEPHARITIS**

This inflammation of the lid margins is characterized by erythema and crust or scaling; the usual symptoms are irritation, burning, and itching. The condition is commonly bilateral and chronic or recurrent. The 2 main types are *staphylococcal* and *seborrheic*. In staphylococcal blepharitis, ulceration of the lid margin is common, the lashes tend to fall out, and conjunctivitis and superficial keratitis are often associated. In seborrheic blepharitis, the scales tend to be greasy; the lid margins are less red, and ulceration usually does not occur. The blepharitis is often of mixed type.

Thorough daily cleansing of the lid margins with a cloth or moistened cotton applicator to remove scales and crusts is important in the treatment of both forms. Staphylococcal blepharitis is treated with an antibiotic. The treatment of seborrheic blepharitis includes an antistaphylococcal antibiotic applied directly to the lid margins. When a child also has seborrhea, concurrent treatment of the scalp is important.

Pediculosis of the eyelashes may produce a clinical picture of blepharitis. The lice can be smothered with ophthalmic-grade petrolatum ointment applied to the lid margin and lashes. Nits should be mechanically removed from the lashes. It should be remembered that pediculosis can represent a sexually transmitted disease. Molluscum virus involvement of the lids can also cause blepharitis.

**HORDEOLUM (STYE)**

Infection of the glands of the lid may be acute or subacute; tender focal swelling and redness are noted. The usual agent is *Staphylococcus aureus*. When the meibomian glands are involved, the lesion is referred to as an internal hordeolum; the abscess tends to be large and may point through either the skin or the conjunctival surface. When the infection involves the glands of Zeis or Moll, the abscess tends to be smaller and more superficial and points at the lid margin; it is then referred to as an external hordeolum or stye.

Treatment is frequent warm compresses and, if necessary, surgical incision and drainage. In addition, topical antibiotic preparations are often used. Untreated, the infection may progress to cellulitis of the lid or orbit, requiring the use of systemic antibiotics.

**CHALAZION**

A chalazion is a granulomatous inflammation of a meibomian gland characterized by a firm, nontender nodule in the upper or lower lid. This lesion tends to be chronic and differs from internal hordeolum in the absence of acute inflammatory signs. Although many chalazia subside spontaneously, excision may be necessary if they become large enough to distort vision (by inducing astigmatism by exerting pressure on the globe) or to be a cosmetic blemish. Patients who experience frequent chalazia formation, or those who have significant corneal changes secondary to the underlying blepharitis,
may benefit from systemic, low-dose erythromycin or azithromycin treatment.

**COLOBOMA OF THE EYELID**
This cleft-like deformity may vary from a small indentation or notch of the free margin of the lid to a large defect involving almost the entire lid. If the gap is extensive, ulceration and corneal opacities may result from exposure. Early surgical correction of the lid defect is recommended. Other deformities frequently associated with lid colobomas include dermoid cysts or dermolipomas on the globe; they often occur in a position corresponding to the site of the lid defect. Lid colobomas may also be associated with extensive facial malformation, as in mandibulofacial dysostosis (Franceschetti or Treacher Collins syndrome).

**TUMORS OF THE LID**
A number of lid tumors arise from surface structures (the epithelium and sebaceous glands). Nevi may appear in early childhood; most are junctional. Compound nevi tend to develop in the prepubertal years and dermal nevi at puberty. Malignant epithelial tumors (basal cell carcinoma, squamous cell carcinoma) are rare in children, but the basal cell nevus syndrome and the malignant lesions of xeroderma pigmentosum and of Rothmund-Thomson syndrome may develop in childhood.

Other lid tumors arise from deeper structures (the neural, vascular, and connective tissues). Capillary hemangiomas are especially common in children (Fig. 624-2). Many tend to regress spontaneously, although they may show alarmingly rapid growth in infancy. In many cases, the best management of such hemangiomas is patient observation, allowing spontaneous regression to occur (see Chapter 650). In the case of a rapidly expanding lesion, which may cause amblyopia by obstructing the visual axis or inducing astigmatism, corticosteroid, interferon, or surgical treatment should be considered. Systemic propranolol has been shown to be an effective treatment without the risks associated with corticosteroid use. Other treatment options include corticosteroids, systemically or by direct injection, and surgical excision. Nevus flammeus (port-wine stain), a noninvoluting hemangioma, occurs as an isolated lesion or in association with other signs of Sturge-Weber syndrome. Affected patients should be monitored for the development of glaucoma. Lymphangiomas of the lid appear as firm masses at or soon after birth and tend to enlarge slowly during the growing years. Associated conjunctival involvement, appearing as a clear, cystic, sinuous conjunctival mass, may provide a clue to the diagnosis. In some cases, there is also orbital involvement. The **treatment** is surgical excision.

Plexiform neuromas of the lids occur in children with neurofibromatosis, often with ptosis as the first sign. The lid may take on an S-shaped configuration. The lids may also be involved by other tumors, such as retinoblastoma, neuroblastoma, and rhabdomyosarcoma of the orbit; these conditions are discussed elsewhere.

*Bibliography is available at Expert Consult.*

![Figure 624-2 Capillary hemangioma of the eyelid. (Courtesy of Amy Nopper, MD, and Brandon Newell, MD.)*](image)
**Bibliography**


THE TEAR FILM
This film, which bathes the eye, is actually a complex structure composed of 3 layers. The innermost mucin layer is secreted by the goblet and epithelial cells of the conjunctiva and the acinar cells of the lacrimal gland. It adds stability and provides an attachment for the tear film to the conjunctiva and cornea. The middle aqueous layer constitutes 98% of the tear film and is produced by the main lacrimal gland and accessory lacrimal glands. It contains various electrolytes and proteins as well as antibodies. The outermost lipid layer is produced largely from the sebaceous meibomian glands of the eyelid and retards evaporation of the tear film. Tears drain medially into the punctal openings of the lid margin and flow through the canaliculi into the lacrimal sac and then through the nasolacrimal duct into the nose (Fig. 625-1). Preterm infants have reduced tear secretion. This may mask the diagnosis of a nasolacrimal duct obstruction and concentrate topically applied medications. Tear production reaches adult levels near term.
DACRYOSTENOSIS

Congenital nasolacrimal duct obstruction (CNLDO), or dacryostenosis, is the most common disorder of the lacrimal system, occurring in up to 20% of newborn infants. It is usually caused by a failure of canalization of the epithelial cells that form the nasolacrimal duct as it enters the nose (valve of Hasner). Signs of CNLDO may be present at the time of birth, although the condition may not become evident until normal tear production develops. Signs of CNLDO include an excessive tear lake, overflow of tears onto the lid and cheek, and reflux of mucoid material that is produced in the lacrimal sac. Erythema or maceration of the skin may result from irritation and rubbing produced by dripping of tears and discharge. If the blockage is complete, these signs may be severe and continuous. If obstruction is only partial, the nasolacrimal duct may be capable of draining the basal tear film that is produced. However, under periods of increased tear production (exposure to cold, wind, sunlight) or increased closure of the distal end of the nasolacrimal duct (nasal mucosal edema), tear overflow may become evident or may increase.

Infants at increased risk for CNLDO include those with trisomy 21, EEC (ectodactyly, ectodermal dysplasia, clefting) syndrome, branchiooculofacial syndrome, craniofacial dysmorphism, or Goldenhar syndrome. Infants with CNLDO may develop acute infection and inflammation of the nasolacrimal sac (dacryocystitis), inflammation of the surrounding tissues (pericystitis), or, rarely, periorbital cellulitis. With dacryocystitis, the sac area is swollen, red, and tender, and patients may have systemic signs of infection such as fever and irritability.

The primary treatment of uncomplicated nasolacrimal duct obstruction is a regimen of nasolacrimal massage, usually 2-3 times daily, accompanied by cleansing of the lids with warm water. Topical antibiotics are used for control of mucopurulent drainage. A bland ophthalmic ointment may be used on eyelids if the skin is macerated. Most cases of CNLDO resolve spontaneously; 96% before 1 yr of age. For cases that do not resolve by 1 yr, the nasolacrimal duct may be probed in the office with topical anesthesia, with a cure rate of approximately 80%. Some ophthalmologists intubate the nasolacrimal system at the same time as this has been shown to improve the outcome of the procedure.

Acute dacryocystitis or cellulitis requires prompt treatment with systemic antibiotics. In such cases, some form of definitive surgical intervention is usually indicated.

A dacryocystocele (mucocele) is an unusual presentation of a non-patent nasolacrimal sac that is obstructed both proximally and distally. Dacryocystoceles can be seen at birth or shortly after birth as a bluish subcutaneous mass just below the medial canthal tendon (Fig. 625-2).

Initial treatment of dacryocystocele is usually conservative, involving massage/digital decompression of the lacrimal sac. If resolution of the dacryocystocele is not achieved with conservative management, the surgical probing may be beneficial. At times, the intranasal portion of the nasolacrimal duct becomes distended, causing respiratory compromise. In a recent study, 9.5% of infants with dacryocystocele had related respiratory compromise. These infants benefit from early probing. Another associated complication of dacryocystocele is that of dacryocystitis/cellulitis. This requires systemic antibiotics, often with hospitalization. In the aforementioned study, 65% of infants with dacryocystocele developed dacryocystitis/cellulitis. Once the cellulitis has improved, the nasolacrimal system should be probed if spontaneous resolution has not occurred.

Not all tearing in infants and children is caused by nasolacrimal obstruction. Tearing may also be a sign of glaucoma, intraocular inflammation, or external irritation, such as that from a corneal abrasion or foreign body.

ALACRIMA AND “DRY EYE”

Alacrima refers to a wide spectrum of disorders with reduced or absent tear secretion. Occasionally, normal basal tearing occurs with an absence of emotional tearing. Etiologies can be divided into syndromes that have a pathologic association or are inherited. Associated syndromes include familial dysautonomia (Riley-Day syndrome), anhidrotic ectodermal dysplasia, and triple-A syndrome (Allgrove syndrome). Examples of pathologic association include aplasia of cranial nerve nuclei and lacrimal gland aplasia/hypoplasia. Both autosomal recessive and autosomal dominant inheritance has been reported in isolated congenital alacrima. In addition, medications with anticholinergic side effects can decrease tear production. The patients with alacrima have variable presentation including no symptoms, photophobia, foreign body sensation, eye pain, and decreased vision. The symptoms, if present, often occur early in life. Because the dryness can be severe, damage to the cornea and subsequent loss of vision may occur. The goal of treatment is to minimize corneal irritation, corneal scarring, and loss of vision. Aggressive ocular lubrication is used to prevent these sequelae.

An acquired abnormality of any layer of the tear film may produce a dry eye. Commonly acquired disorders that may lead to a decreased or unstable tear film include Sjögren syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, vitamin A deficiency, viral infections of the lacrimal gland, ocular pemphigoid, trachoma, chemical burns, irradiation, isotretinoin treatment of acne, graft-versus-host disease, and meibomian gland dysfunction. Exposure as a consequence of poor lid closure or other pathologic states can quickly lead to pathologically dry eyes. Examples of conditions leading to such exposure include ichthyosis, xeroderma pigmentosum, and certain craniosynostoses syndromes such as Crouzon, Apert, or Pfeiffer. Any tear deficiency can lead to corneal ulceration, scarring, or infection. Treatment includes correction of the underlying disorder when possible and frequent instillation of an ocular lubricant. In some cases, occlusion of the lacrimal puncta is helpful. In severe cases, tarsorrhaphy may be necessary to protect the cornea.

Bibliography is available at Expert Consult.
Bibliography


CONJUNCTIVITIS
The conjunctiva reacts to a wide range of bacterial and viral agents, allergens, irritants, toxins, and systemic diseases. Conjunctivitis is common in childhood and may be infectious or noninfectious. The differential diagnosis of a red-appearing eye includes conjunctival as well as other ocular sites (Table 626-1).
**Table 626-1  The Red Eye**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ETIOLOGY</th>
<th>SIGNS AND SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial conjunctivitis</td>
<td>Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis</td>
<td>Mucopurulent unilateral or bilateral discharge, normal vision, photophobia</td>
<td>Topical antibiotics, parenteral ceftriaxone for gonococcus, H. influenzae</td>
</tr>
<tr>
<td>Hyperacute bacterial conjunctivitis</td>
<td>Neisseria gonorrhoeae, Neisseria meningitides</td>
<td>Conjunctival injection and edema (chemosis); gritty sensation</td>
<td></td>
</tr>
<tr>
<td>Viral conjunctivitis</td>
<td>Adenovirus, ECHO virus, coxsackievirus, herpes simplex virus</td>
<td>As above; may be hemorrhagic, unilateral</td>
<td>Self-limited</td>
</tr>
<tr>
<td>Neonatal conjunctivitis</td>
<td>Chlamydia trachomatis, gonococcus, chemical (silver nitrate), S. aureus</td>
<td>Palpebral conjunctival follicle or papillae; as above</td>
<td>Ceftriaxone for gonococcus and erythromycin for C. trachomatis</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>Seasonal pollens or allergen exposure</td>
<td>Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae</td>
<td>Antihistamines, topical mast cell stabilizers or prostaglandin inhibitors, steroids</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Herpes simplex virus, adenovirus, S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba, chemicals</td>
<td>Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection</td>
<td>Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>S. aureus, S. pneumoniae, Candida albicans, associated surgery or trauma</td>
<td>Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Anterior uveitis (iritis)</td>
<td>JIA, postinfectious with arthritis and rash, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease</td>
<td>Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions, pain, photophobia, small pupil, poor vision</td>
<td>Topical steroids, plus therapy for primary disease</td>
</tr>
<tr>
<td>Posterior uveitis (choriitis)</td>
<td>Toxoplasmosis, histoplasmosis, Toxocara canis</td>
<td>No signs of erythema, decreased vision</td>
<td>Specific therapy for pathogen</td>
</tr>
<tr>
<td>Episcleritis/scleritis</td>
<td>Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura)</td>
<td>Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation</td>
<td>Episcleritis is self-limiting; topical steroids for fast relief</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Occupational exposure</td>
<td>Unilateral, red, gritty feeling; visible or microscopic size</td>
<td>Irrigation, removal; check for ulceration</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>S. aureus, Staphylococcus epidermidis, seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, Pseudomonas, Acanthamoeba, chemicals</td>
<td>Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins</td>
<td>Topical antibiotics, warm compresses, lid hygiene</td>
</tr>
<tr>
<td>Dacryocystitis</td>
<td>Obstructed lacrimal sac: S. aureus, H. influenzae, pneumococcus</td>
<td>Pain, tenderness, erythema, and exudates in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis</td>
<td>Systemic, topical antibiotics; surgical drainage</td>
</tr>
<tr>
<td>Dacryoadenitis</td>
<td>S. aureus, Streptococcus, CMV, measles, EBV, enteroviruses; trauma, sarcoidosis, leukemia</td>
<td>Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis</td>
<td>Systemic antibiotics; drainage of orbital abscesses</td>
</tr>
<tr>
<td>Orbital cellulitis (postseptal)</td>
<td>Paranasal sinusitis: H. influenzae, S. aureus, S. pneumoniae, streptococci</td>
<td>Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis</td>
<td>Systemic antibiotics, drainage of orbital abscesses</td>
</tr>
<tr>
<td>Periorbital cellulitis (preseptal)</td>
<td>Trauma: S. aureus, Streptococcus</td>
<td>Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance</td>
<td>Systemic antibiotics</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

Ophthalmia Neonatorum

This form of conjunctivitis, occurring in infants younger than 4 wk of age, is the most common eye disease of newborns. Its many different causal agents vary greatly in their virulence and outcome. Silver nitrate instillation may result in a mild self-limited chemical conjunctivitis, whereas Neisseria gonorrhoeae and Pseudomonas are capable of causing corneal perforation, blindness, and death. The risk of conjunctivitis in newborns depends on frequencies of maternal infections, prophylactic measures, circumstances during labor and delivery, and postdelivery exposure to microorganisms.

Epidemiology

 Conjunctivitis during the neonatal period is usually acquired during vaginal delivery and reflects the sexually transmitted infections prevalent in the community. In 1880, 10% of European children developed gonococcal conjunctivitis at birth. Ophthalmia neonatorum was the leading cause of blindness during that period. The epidemiology of this condition changed dramatically in 1881, when Crede reported that 2% silver nitrate solution instilled in the eyes of newborns reduced the incidence of gonococcal ophthalmia from 10% to 0.3%.

 During the 20th century, the incidence of gonococcal ophthalmia neonatorum decreased in industrialized countries secondary to widespread use of silver nitrate prophylaxis and prenatal screening and treatment of maternal gonorrhea. Gonococcal ophthalmia neonatorum has an incidence of 0.3/1,000 live births in the United States. In comparison, Chlamydia trachomatis is the most common organism causing ophthalmia neonatorum in the United States, with an incidence of 8.2/1,000 births.

Clinical Manifestations

 The clinical manifestations of the various forms of ophthalmia neonatorum are not specific enough to allow an accurate diagnosis. Although the timing and character of the signs are somewhat typical for each cause of this condition, there is considerable overlap and physicians should not rely solely on clinical findings. Regardless of its cause, ophthalmia neonatorum is characterized by redness and chemosis (swelling) of the conjunctiva, edema of the eyelids, and discharge, which may be purulent.

Neonatal conjunctivitis is a potentially blinding condition. The infection may also have associated systemic manifestations that require treatment. Therefore, any newborn infant who develops signs of conjunctivitis needs a prompt and comprehensive systemic and ocular evaluation to determine the agent causing the infection and the appropriate treatment.

 The onset of inflammation caused by silver nitrate drops usually occurs within 6-12 hr after birth, with clearing by 24-48 hr. The usual incubation period for conjunctivitis caused by N. gonorrhoeae is 2-5 days, and for that caused by C. trachomatis, 5-14 days. Gonococcal infection may be present at birth or be delayed beyond 5 days of life owing to partial suppression by ocular prophylaxis. Gonococcal conjunctivitis may also begin in infancy after inoculation by the contaminated fingers of adults. The time of onset of disease with other bacteria is highly variable.

Gonococcal conjunctivitis begins with mild inflammation and a serosanguineous discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If proper treatment is delayed, the infection may spread to involve the deeper layers of the conjunctivae and the cornea. Complications include corneal ulceration and perforation, iridocyclitis, anterior synechiae, and rarely panophthalmitis. Conjunctivitis caused by C. trachomatis (inclusion blennorrhea) may vary from mild inflammation to severe swelling of the eyelids with copious purulent discharge. The process involves mainly the tarsal conjunctivae; the corneas are rarely affected. Conjunctivitis caused by Staphylococcus aureus or other organisms is similar to that produced by C. trachomatis. Conjunctivitis caused by Pseudomonas aeruginosa is uncommon, acquired in the nursery, and a potentially serious process. It is characterized by the appearance on days 5-18 of edema, erythema of the lids, purulent discharge, pannus formation, endophthalmitis, sepsis, shock, and death.

Diagnosis

 Conjunctivitis appearing after 48 hr should be evaluated for a possibly infectious cause. Gram stain of the purulent discharge should be performed and the material cultured. If a viral cause is suspected, a swab should be submitted in tissue culture media for virus isolation. In chlamydial conjunctivitis, the diagnosis is made by examining Giemsa-stained epithelial cells scraped from the tarsal conjunctivae for the characteristic intracytoplasmic inclusions, by isolating the organisms from a conjunctival swab using special tissue culture techniques, by immunofluorescent staining of conjunctival scrapings for chlamydial inclusions, or by tests for chlamydial antigen or DNA. The differential diagnosis of ophthalmia neonatorum includes dactylocystitis caused by congenital nasolacrimal duct obstruction with lacrimal sac distention (dacryocystocele; see Chapter 625).

Treatment

 Treatment of infants in whom gonococcal ophthalmia is suspected and the Gram stain shows the characteristic intracellular Gram-negative diplococci should be initiated immediately with ceftriaxone, 50 mg/kg/24 hr for 1 dose, not to exceed 125 mg. The eye should also be irrigated initially with saline every 10-30 min, gradually increasing to 2-hr intervals until the purulent discharge has cleared. An alternative regimen includes cefotaxime (100 mg/kg/24 hr given IV or IM every 12 hr for 7 days or 100 mg/kg as a single dose). Treatment is extended if sepsis or other extraocular sites are involved (meningitis, arthritis).

Neonatal conjunctivitis secondary to chlamydial infections is treated with oral erythromycin (50 mg/kg/24 hr in 4 divided doses) for 2 wk. This cures conjunctivitis and may prevent subsequent chlamydial pneumonia. Pseudomonas neonatal conjunctivitis is treated with systemic antibiotics, including an aminoglycoside plus local saline irrigation and gentamicin ophthalmic ointment. Staphylococcal conjunctivitis is treated with parenteral methicillin and local saline irrigation.

Prognosis and Prevention

 Before the institution of topical ophthalmic prophylaxis at birth, gonococcal ophthalmia was a common cause of blindness or permanent eye damage. If properly applied, this form of prophylaxis is highly effective unless infection is present at birth. Drops of 0.5% erythromycin or 1% silver nitrate are instilled directly into the open eyes at birth using wax or plastic single-dose containers. Saline irrigation after silver nitrate application is unnecessary. Silver nitrate is ineffective against active infection and may have limited use against Chlamydia. Povidone-iodine (2% solution) may also be an effective prophylactic agent, especially in developing countries.

 Identification of maternal gonococcal infection and appropriate treatment has become a standard element of routine prenatal care. An infant born to a woman who has untreated gonococcal infection should receive a single dose of ceftriaxone, 50 mg/kg (maximum 125 mg) IV or IM, in addition to topical prophylaxis. The dose should be reduced for premature infants. Penicillin (50,000 units) should be used if the mother’s gonococcal isolate is known to be penicillin sensitive.

 Neither topical prophylaxis nor topical treatment prevents the afebrile pneumonia that occurs in 10-20% of infants exposed to C. trachomatis. Although chlamydial conjunctivitis is often a self-limiting disease, chlamydial pneumonia may have serious consequences. It is important that infants with chlamydial disease receive systemic treatment. Treatment of colonized pregnant women with erythromycin may prevent neonatal disease.

Acute Purulent Conjunctivitis

 This is characterized by more or less generalized (bilateral in 50-75%) conjunctival hyperemia, edema, mucopurulent exudate, glazed eyes (lids stuck together after sleeping), and various degrees of ocular pain and discomfort. It is usually a result of bacterial infection. In addition, there is usually little or no pruritus or periauricular lymph node enlargement; the peak season is between December and April. Bacterial conjunctivitis is more common in young children (<5 yr), whereas viral conjunctivitis is more common among adults. The most frequent causes are nontypeable Haemophilus influenzae (60-80%) (associated
Topical Antibiotics Used to Treat Bacterial Conjunctivitis: Adult Dosages

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacitracin (AK-Tracin, Bactricin) ointment</td>
<td>Apply 0.5 inch in eye q3-4h</td>
</tr>
<tr>
<td>Ciprofloxacin (Ciloxan) 0.3% ophthalmic solution</td>
<td>1-2 gtt in eye q15min × 6h, then q30min × 18h, then q1h × 1 day, then q4h × 12 days*</td>
</tr>
<tr>
<td>Gatifloxacin (Zymar) 0.3% ophthalmic solution</td>
<td>Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4h</td>
</tr>
<tr>
<td>Gentamicin (Gentak, Gentasol) 0.3% ophthalmic solution or ointment</td>
<td>1 gt in eye q2h up to 8 × per day × 2 days, then 1 gt qid × 5 days</td>
</tr>
<tr>
<td>Levofloxacin (Quixin) 0.5% ophthalmic solution</td>
<td>Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4h</td>
</tr>
<tr>
<td>Neomycin/polymyxin B/gramicidin (Neosporin) ophthalmic solution</td>
<td>1-2 gtt in eye q4h × 7-10 days</td>
</tr>
<tr>
<td>Ofloxacin (Ocuflox) 0.3% ophthalmic solution</td>
<td>Ointment: 0.5-inch ribbon in eye q3-4h and qhs 70.</td>
</tr>
<tr>
<td>Polymyxin B and trimethoprim (Polytrim) ophthalmic solution</td>
<td>1-2 gtt in eye q4h × 7-10 days</td>
</tr>
<tr>
<td>Sulfacetamide (Isopto Cetamide, Ocusulf-10, Sodium Sulamyd, Sulf-10, AK-Sulf) 10% ophthalmic solution, ointment</td>
<td>1-2 gtt in eye q2-4h × 2 days, then 1-2 gtt in eye qid × 5 days</td>
</tr>
<tr>
<td>Tobramycin (AK-Tob, Tobrex) 0.3% ophthalmic solution</td>
<td>1-2 gtt in eye q4h</td>
</tr>
</tbody>
</table>

*Exceeds dosage recommended by the manufacturer.


with ipsilateral otitis media), pneumococci (20%), and staphylococci (3-10%). Bacterial purulent conjunctivitis, especially that caused by pneumococcus or H. influenzae, may occur in epidemics. Conjunctival smear and culture are helpful in differentiating specific types. These common forms of acute purulent conjunctivitis usually respond well to warm compresses and topical instillation of antibiotic drops, which shortens the duration of illness and hastens return to school. Topical antibiotics include aminoglycosides (gentamicin, tobramycin), quinolones (ciprofloxacin, ofloxacin, moxifloxacin), and combinations of antibiotics and chloramphenicol. Hyperacute bacterial conjunctivitis is caused by gonococcal or meningococcal infection and requires systemic, not topical, antimicrobial therapies. Concerning symptoms that should require an ophthalmology referral include vision loss, severe purulent discharge, corneal involvement, conjunctival scarring, cutaneous-conjunctival involvement (Stevens-Johnson syndrome), recurrent symptoms, severe pain, herpes simplex virus infection, severe photophobia, and involvement with a contact (cosmetic or prescription) lens.

Viral Conjunctivitis

This is generally characterized by a watery discharge. Follicular changes (small aggregates of lymphocytes) are often found in the palpebral conjunctiva. Involvement is often unilateral and associated with periauricular nodes. Viral conjunctivitis occurs more often in the summer and in older children (>5 yr). Conjunctivitis resulting from adenovirus infection is relatively common, sometimes with corneal involvement as well as pharyngitis or pneumonia. Outbreaks of conjunctivitis caused by enterovirus are also encountered; this type may be hemorrhagic. Acute hemorrhagic conjunctivitis may be epidemic because of enterovirus CA24 or 70 and is characterized by red, swollen, and painful eyes with a hemorrhagic watery discharge. Conjunctivitis is commonly associated with such systemic viral infections as the childhood exanthems, particularly measles. Viral conjunctivitis is usually self-limited.

Epidemic Keratoconjunctivitis

This is caused by adenovirus type 8 and is transmitted by direct contact. It initially presents as a sensation of a foreign body beneath the lids, with itching and burning. Edema (chemosis) and photophobia develop rapidly, and large oval follicles appear within the conjunctiva. Preauricular adenopathy and a pseudomembrane on the conjunctival surface occur frequently. Subepithelial corneal infiltrates may develop and may cause blurring of vision; these usually disappear but may permanently reduce visual acuity. Corneal complications are less common in children than in adults. Children may have associated upper respiratory tract infection and pharyngitis. No specific medical therapy is available to decrease the symptoms or shorten the course of the disease. Emphasis must be placed on prevention of spread of the disease. Replicating virus is present in 95% of patients 10 days after the appearance of symptoms.

Pharyngoconjunctival fever presents with high fever, pharyngitis, bilateral conjunctivitis, and periocular lymphadenopathy. It is highly contagious.

Membranous and Pseudomembranous Conjunctivitis

These types of conjunctivitis can be encountered in a number of diseases. The classic membranous conjunctivitis is that of diphtheria, accompanied by a fibrin-rich exudate that forms on the conjunctival surface and permeates the epithelium; the membrane is removed with difficulty and leaves raw bleeding areas. In pseudomembranous conjunctivitis, the layer of fibrin-rich exudate is superficial and can often be stripped easily, leaving the surface smooth. This type occurs with many bacterial and viral infections, including staphylococcal, pneumococcal, streptococcal, or chlamydial conjunctivitis, and in epidemic keratoconjunctivitis. It is also found in vernal conjunctivitis and in Stevens-Johnson disease.
Allergic Conjunctivitis
This is usually accompanied by intense itching, clear watery discharge, and conjunctival edema (chemosis). It is commonly seasonal (spring-summer). Cold compresses and topical antihistamine drops give symptomatic relief. Topical mast cell stabilizers or prostaglandin inhibitors may also help. In selected cases, topical corticosteroids are used under an ophthalmologist's supervision but should not be used routinely or for a long time.

Vernal Conjunctivitis
This usually begins in the prepubertal years and may recur for many years. Atopy appears to have a role in its origin, but the pathogenesis is uncertain. Extreme itching and tearing are the usual complaints. Large, flattened, cobblestone-like papillary lesions of the palpebral conjunctiva are characteristic (Fig. 626-2). A stringy exudate and a milky conjunctival pseudomembrane are frequently present. Small elevated lesions of the bulbar conjunctiva adjacent to the limbus (limbal form) may be found. Smear of the conjunctival exudate reveals many eosinophils. Topical corticosteroid therapy and cold compresses afford some relief. Topical mast cell stabilizers or prostaglandin inhibitors are useful when long-term control is needed. The long-term use of corticosteroids should be avoided.

Parinaud Oculoglandular Syndrome
This represents a form of cat-scratch disease and is caused by Bartonella henselae, which is transmitted from cat to cat by fleas (see Chapter 209). Kittens are more likely than adult cats to be infected. Humans can become infected when they are scratched by a cat. In addition, bacteria may pass from a cat's saliva to its fur during grooming. The bacteria can become infected when they are scratched by a cat. In addition, bacteria may pass from a cat's saliva to its fur during grooming. The bacteria can then be deposited on the conjunctiva after rubbing one's eyes after handling the cat. Lymphadenopathy and conjunctivitis are hallmarks of the disease. Conjunctival granulomas may develop (Fig. 626-3). The course is generally self-limited, but antibiotics may be used in some cases.

Chemical Conjunctivitis
This can result when an irritating substance enters the conjunctival sac (as in the acute but benign conjunctivitis caused by silver nitrate in newborns). Other common offenders are household cleaning substances, sprays, smoke, smog, and industrial pollutants. Alkalies tend to linger in the conjunctival tissues and continue to inflict damage for hours or days. Acids precipitate the proteins in tissues and so produce their effect immediately. In either case, prompt, thorough, and copious irrigation is crucial. Extensive tissue damage, even loss of the eye, can result, especially if the offending agent is an alkali.

Other Conjunctival Disorders
Subconjunctival hemorrhage is manifested by bright or dark red patches in the bulbar conjunctiva and may result from injury or inflammation. It commonly occurs spontaneously. It may occasionally result from severe sneezing or coughing. Rarely, it may be a manifestation of a blood dyscrasia. Subconjunctival hemorrhages are self-limiting and require no treatment.

Pterygium is a fleshy triangular conjunctival lesion that may encroach on the cornea. It typically occurs in the nasal interpalpebral region. The pathologic findings are similar to those of a pinguecula. The development of pterygia is related to exposure to ultraviolet light, and it therefore is more commonly found among people who live near the equator. Removal is suggested when the lesion encroaches far onto the cornea. Recurrence after removal is common.

Dermoid cyst and dermolipoma are benign lesions, clinically similar in appearance. They are smooth, elevated, round to oval lesions of various sizes. The color varies from yellowish white to fleshy pink. The most frequent site is the upper outer quadrant of the globe; they also commonly occur near or straddling the limbus. Dermolipoma is composed of adipose and connective tissue. Dermoid cysts may also contain glandular tissue, hair follicles, and hair shafts. Excision for cosmetic reasons is feasible. Dermolipomas are often connected to the extraocular muscles, making their complete removal impossible without sacrificing ocular motility.

Conjunctival nevus is a small, slightly elevated lesion that may vary in pigmentation from pale salmon to dark brown. It is usually benign, but careful observation for progressive growth or changes suggestive of malignancy is advised.

Symblepharon is a cicatricial adhesion between the conjunctiva of the lid and the globe; the lower lid is usually affected. It follows operation or injuries, especially burns from lye, acids, or molten metals. It is a serious complication of Stevens-Johnson syndrome. It may interfere with motion of the eyeball and may cause diplopia. The adhesions should be separated and the raw surfaces kept from uniting during healing. Grafts of oral mucous membrane may be necessary.

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Bibliography
Abnormalities of the Cornea

Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

MEGALOCORNEA
This is a nonprogressive symmetric condition characterized by an enlarged cornea (>12 mm in diameter) and an anterior segment in which there is no evidence of previous or concurrent ocular hypertension. High myopia is frequently present and may lead to reduced vision. A frequent complication is the development of lens opacities in adult life. All modes of inheritance have been described, although X-linked recessive is the most common; therefore, this disorder more commonly affects males. Systemic abnormalities that may be associated with megalocornea include Marfan syndrome, craniosynostosis, and Alport syndrome. The cause of the enlargement of the cornea and the anterior segment is unknown, but possible explanations include a defect in the growth of the optic cup and an arrest of congenital glaucoma. The region on the X chromosome responsible for this disorder has been identified.

Pathologic corneal enlargement caused by glaucoma is to be differentiated from this anomaly. Any progressive increase in the size of the cornea, especially when accompanied by photophobia, laceration, or haziness of the cornea, requires prompt ophthalmologic evaluation.

MICROCORNEA
Microcornea, or anterior microphthalmia, is an abnormally small cornea in an otherwise relatively normal eye. It may be familial, with transmission being dominant more often than recessive. More commonly, a small cornea is just one feature of an otherwise developmentally abnormal or microphthalmic eye; associated defects include colobomas, microphakia, congenital cataract, glaucoma, and aniridia.

KERATOCONUS
This is a disease of unclear pathogenesis characterized by progressive thinning and bulging of the central cornea, which becomes cone shaped. Although familial cases are known, most cases are sporadic. It is a common ocular condition with an incidence of 1 in 2,000 adults. Eye rubbing and contact lens wear have been implicated as pathogenic, but the evidence to support this is equivocal. The incidence is increased in individuals with atopy, Down syndrome, Marfan syndrome, and retinitis pigmentosa.

Most cases are bilateral, but involvement may be asymmetric. The disorder usually presents and progresses rapidly during adolescence; progression slows and stabilizes when patients reach full growth. Descemet membrane may occasionally be stretched beyond its elastic breaking point, causing an acute rupture in the membrane with resultant sudden and marked corneal edema (acute hydrops, Fig. 627-1) and decrease in vision. The corneal edema resolves as endothelial cells cover the defective area. Some degree of corneal scarring occurs, but the visual acuity is often better than before the initial incident. Signs of keratoconus include Munson sign (bulging of the lower eyelid on looking downward) and the presence of a Fleischer ring (a deposit of iron in the epithelium at the base of the cone). Glasses and contact lenses are the first step in treating the visual distortion caused by keratoconus. Emerging research now suggests that a corneal cross-linking procedure using riboflavin and UV light may arrest the progression of keratoconus. If the cornea vaults too severely for the vision to be corrected with contact lenses then a corneal transplant must be performed to restore vision.

NEONATAL CORNEAL OPACITIES
Loss of the normal transparency of the cornea in neonates may occur secondary to either intrinsic hereditary or extrinsic environmental causes (Table 627-1).

SCLEROCORNEA
In sclerocornea, the normally translucent cornea is replaced by scleral-like tissue. Instead of a clearly demarcated cornea, white, feathery, often ill-defined and vascularized tissue develops in the peripheral cornea, appearing to blend with and extend from the sclera. The central cornea is usually clearer, but total replacement of the cornea with sclera may occur. The curvature of the cornea is often flatter, similar to the sclera. Potentially coexisting abnormalities include a shallow anterior chamber, iris abnormalities, and microphthalmos. This condition is usually bilateral. In approximately 50% of cases, a dominant or recessive inheritance has been described. Sclerocornea has been reported in association with numerous systemic abnormalities including limb deformities, craniofacial defects, and genitourinary disorders. In generalized sclerocornea, especially if bilateral, early corneal transplantation should be considered in an effort to provide vision.

Sclerocornea is classified into one of the congenital corneal opacity disorders with cornea plana if it involves peripheral scleralization or total sclerocornea disorders such as Peters anomaly.

PETE'S ANOMALY
Peters anomaly is a central corneal opacity (leukoma) that is present at birth (Fig. 627-2). It is often associated with iridocorneal adhesions that extend from the iris collarette to the border of the corneal opacity. Approximately 50% of patients have other ocular abnormalities, which may include cataracts, glaucoma, and microcornea. As many as 80% of cases may be bilateral and 60% are associated with systemic malformations (Peters plus syndrome) that may include short stature, developmental delay, dysmorphic facial features, and cardiac, genitourinary, and central nervous system malformations. Some investigators have divided Peters anomaly into 2 types: a mesodermal or neuroectodermal form (type I), which does not show associated lens changes, and a surface ectodermal form (type II), which does. Histologic findings include a focal absence of Descemet membrane and corneal endothelium in the region of the opacity. Peters anomaly may be caused by incomplete migration and differentiation of the precursor cells of the central corneal endothelium and Descemet membrane or a defective separation between the primitive lens and cornea during embryogenesis.
<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>LATERALITY</th>
<th>OPACITY</th>
<th>OCULAR PRESSURE</th>
<th>OTHER OCULAR ABNORMALITIES</th>
<th>NATURAL HISTORY</th>
<th>INHERITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S—Sclerocornea</strong></td>
<td>Unilateral or bilateral</td>
<td>Vascularized, blends with sclera, clearer centrally</td>
<td>Normal (or elevated)</td>
<td>Cornea plana</td>
<td>Nonprogressive</td>
<td>Sporadic</td>
</tr>
<tr>
<td><strong>T—Tears in endothelium</strong></td>
<td>Unilateral</td>
<td>Diffuse edema</td>
<td>Normal</td>
<td>Possible hyphema, periorbital ecchymoses</td>
<td>Spontaneous improvement in 1 mo</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>Unilateral</td>
<td>Diffuse edema</td>
<td>Normal</td>
<td>Possible hyphema, periorbital ecchymoses</td>
<td>Spontaneous improvement in 1 mo</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Infantile glaucoma</td>
<td>Bilateral</td>
<td>Diffuse edema</td>
<td>Elevated</td>
<td>Megalocornea, photophobia and tearing, abnormal angle</td>
<td>Progressive unless treated</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td><strong>U—Ulcers</strong></td>
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<tr>
<td>Herpes simplex keratitis</td>
<td>Unilateral</td>
<td>Diffuse with geographic epithelial defect</td>
<td>Normal</td>
<td>None</td>
<td>Progressive</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>Bilateral</td>
<td>Disciform or diffuse edema, no frank ulceration</td>
<td>Normal or elevated</td>
<td>Microphtalmos, cataract, pigment epithelial mottling</td>
<td>Stable, may clear</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Neurotrophic exposure</td>
<td>Unilateral or bilateral</td>
<td>Central ulcer</td>
<td>Normal</td>
<td>Lid anomalies, congenital sensory neuropathy</td>
<td>Progressive</td>
<td>Sporadic</td>
</tr>
<tr>
<td><strong>M—Metabolic (rarely present at birth)</strong></td>
<td>Bilateral</td>
<td>Diffuse haze, denser peripherally</td>
<td>Normal</td>
<td>Few</td>
<td>Progressive</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>(mucopolysaccharidoses IH, IS; mucolipidosis type IV)*</td>
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<tr>
<td><strong>P—Posterior corneal defect</strong></td>
<td>Unilateral or bilateral</td>
<td>Central, diffuse haze or vascularized leukemia</td>
<td>Normal or elevated</td>
<td>Anterior chamber cleavage syndrome</td>
<td>Stable, sometimes early clearing or vascularization</td>
<td>Sporadic, autosomal recessive</td>
</tr>
<tr>
<td><strong>E—Endothelial dystrophy</strong></td>
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<td></td>
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</tr>
<tr>
<td>Congenital hereditary endothelial dystrophy</td>
<td>Bilateral</td>
<td>Diffuse corneal edema, marked corneal thickening</td>
<td>Normal</td>
<td>None</td>
<td>Stable</td>
<td>Autosomal dominant or recessive</td>
</tr>
<tr>
<td>Posterior polymorphous dystrophy</td>
<td>Bilateral</td>
<td>Diffuse haze, normal corneal thickness</td>
<td>Normal</td>
<td>Occasional peripheral anterior synechiae</td>
<td>Slowly progressive</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Congenital hereditary stromal dystrophy</td>
<td>Bilateral</td>
<td>Flaky, feathery stromal opacities; normal corneal thickness</td>
<td>Normal</td>
<td>None</td>
<td>Stable</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td><strong>D—Dermoid</strong></td>
<td>Unilateral or bilateral</td>
<td>White vascularized mass, hair, lipid arc</td>
<td>Normal</td>
<td>None</td>
<td>Stable</td>
<td>Sporadic</td>
</tr>
</tbody>
</table>

*Mucopolysaccharidosis IH (Hurler syndrome); mucopolysaccharidosis IS (Scheie syndrome).


**CORNEAL DYSTROPHIES**

These are rare inherited disorders that may present during childhood or early adulthood with bilateral involvement (although severity may be asymmetric) that progresses with time. In most, inheritance is autosomal dominant with variable expression; the most common mutation is in *TGFB1*, which is associated with the granular corneal dystrophy types 1 and 2, as well as lattice corneal dystrophy. Congenital hereditary endothelial dystrophy is both an autosomal recessive (*SLC4A11*) and dominant (unknown gene) disorder; the recessive form presents at birth and is more severe.
may include mechanical debridement of the involved corneal epithelium to remove the source of infection and eliminate an antigenic stimulus to inflammation in the adjacent stroma. Medical treatment involves the use of trifluridine, topical ganciclovir, or systemic acyclovir. In addition, a cycloplegic agent is useful to relieve pain from spasm of the ciliary muscle. Overly aggressive topical antiviral treatment itself can be toxic to the cornea and should be avoided. Recurrent infection and deep stromal involvement can lead to corneal scarring and loss of vision.

Topical use of corticosteroids causes exacerbation of superficial herpetic disease of the eye and may lead to corneal perforation; eyedrops combining steroids and antibiotics are therefore to be avoided in treatment of red eye unless there are clear-cut indications for their use and close supervision during therapy.

Infants born to mothers infected with herpes simplex virus should be examined carefully for signs of ocular involvement. Intravenous acyclovir is required for treatment of ocular herpes in newborns.

CORNEAL ULCERS
The usual signs and symptoms are focal or diffuse corneal haze, hyperemia, lid edema, pain, photophobia, tearing, and blepharospasm. Hypopyon (pus in the anterior chamber) is common. Corneal ulcers require prompt treatment. They result most frequently from contact lens wear and traumatic lesions that become secondarily infected. Many organisms are capable of infecting the cornea. One of the most serious is Pseudomonas aeruginosa; it can rapidly destroy stromal tissue and lead to corneal perforation. Neisseria gonorrhoeae also is particularly damaging to the cornea. Indolent ulcers may be caused by fungi, often in association with the use of contact lenses. In each case, scrapings of the cornea must be studied in an effort to identify the infectious agent and to determine the best therapy. Although aggressive local treatment is generally needed to save the eye, systemic treatment may be necessary in some cases as well. Perforation or scarring resulting from corneal ulceration is an important cause of blindness throughout the world and is estimated to be responsible for 10% of blindness in the United States.

Unexplained corneal ulcers in infants and young children should raise the question of a sensory defect, as in Riley-Day or Goldenhar-Gorlin syndrome, or of a metabolic disorder such as tyrosinemia (Fig. 627-4). Corneal ulceration can also occur as a consequence of severe vitamin deficiencies, such as those seen with cystic fibrosis.

PHLYCTENULES
These are small, yellowish, slightly elevated lesions usually located at the corneal limbus; they may encroach on the cornea and extend centrally. A small corneal ulcer is often found at the head of the advancing lesion, with a fascicle of blood vessels behind the head of the lesion. Although once thought to represent a sign of systemic tuberculcinfection, phlyctenular keratoconjunctivitis is now accepted as a morphologic expression of delayed hypersensitivity to diverse antigens. In children, it commonly occurs as a result of a hypersensitivity reaction to nonpathogenic staphylococcal strains at the eyelid margin. Treatment usually consists of eliminating the underlying disorder, usually staphylococcal blepharitis or meibomianitis, and suppressing the immune response with the use of topical corticosteroid therapy. A superficial stromal pannus and scarring sometimes remain after treatment.

INTERSTITIAL KERATITIS
This denotes nonulcerative inflammation of the corneal stroma. There is a diverse list of causes of interstitial keratitis (IK), including bacterial, viral, parasitic, and inflammatory etiologies. In the United States, herpesvirus infections and congenital syphilis account for the majority of cases of IK. Although the corneal findings may regress with time, "ghost vessels," which represent the previous vascular changes, and patchy corneal scarring remain and serve as permanent stigmata of the disease.

Cogan syndrome is IK associated with hearing loss and vestibular symptoms. Although its cause is unknown, a systemic vasculitis is
suspected. Prompt treatment is required to avoid permanent hearing loss. Both the corneal changes and the auditory involvement may respond to the use of immunosuppressive agents.

CORNEAL MANIFESTATIONS OF SYSTEMIC DISEASE

Several metabolic diseases produce distinctive corneal changes in childhood. Refractile polychromatic crystals are deposited throughout the cornea in cystinosis (see Chapter 85.4). Corneal deposits producing various degrees of corneal haze also occur in certain types of mucopolysaccharidosis (MPS; see Chapter 88), particularly MPS III (Hurler), MPS IS (Scheie), MPS I H/S (Hurler-Scheie compound), MPS IV (Morquio), MPS VI (Maroteaux-Lamy), and sometimes MPS VII (Sly). Corneal deposits may develop in patients with GM1 (generalized) gangliosidosis (see Chapter 86.4). In Fabry disease, fine opacities radiating in a whorl or fan-like pattern occur, and corneal changes can be important in identifying the carrier state (see Chapter 86.4). A spray-like pattern of corneal opacities may also be seen in the Bloch-Sulzberger syndrome (incontinentia pigmenti; see Chapter 596.7). In Wilson disease (see Chapter 357.2), the distinctive corneal sign is the Kayser-Fleischer ring, a golden brown ring in the peripheral cornea resulting from changes in Descemet's membrane. Pigmented corneal rings may develop in neonates with cholestatic liver disease. Corneal changes may occur in autoimmune hypoparathyroidism and band keratopathy in patients with hypercalcaemia (see Chapter 570). Transient keratitis may occur with rubeola and sometimes with rubella (see Chapter 247).

Bibliography is available at Expert Consult.
Bibliography
Chapter 628
Abnormalities of the Lens
Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

CATARACTS
A cataract is any opacity of the lens (Fig. 628-1). Some are clinically unimportant; others significantly affect visual function. The incidence of infantile cataracts is approximately 2-13/10,000 live births. An epidemiologic study of infantile cataracts published in 2003 suggests that approximately 60% of cataracts are an isolated defect; 22% are part of a syndrome; and the remainder are associated with other unrelated major birth defects. Cataracts are more common in low birthweight infants. Infants who weigh at or below 2,500 g have 3-4-fold increased odds of developing infantile cataracts. Some cataracts are associated with other ocular or systemic diseases.

Differential Diagnosis
The differential diagnosis of cataracts in infants and children includes a wide range of developmental disorders, infectious and inflammatory processes, metabolic diseases, and toxic and traumatic insults (Table 628-1). Cataracts may also develop secondary to intraocular processes, such as retinopathy of prematurity, persistent hyperplastic primary vitreous, retinal detachment, retinitis pigmentosa, and uveitis. Finally, a fraction of cataracts in children are inherited (Fig. 628-2).

Developmental Variants
Early developmental processes may lead to various congenital lens opacities. Discrete dots or white plaque-like opacities of the lens capsule are common and sometimes involve the contiguous subcapsular region. Small opacities of the posterior capsule may be associated with persistent remnants of the primitive hyaloid vascular system (the common Mittendorf dot), whereas those of the anterior capsule may be associated with persistent strands of the pupillary membrane or vascular sheath of the lens. Congenital cataracts of this type are usually stationary and rarely interfere with vision, but in some cases, progression occurs.

Prematurity
A special type of lens change seen in some preterm newborn infants is the so-called cataract of prematurity. The appearance is of a cluster of tiny vacuoles in the distribution of the Y sutures of the lens. They

Figure 628-1 Leukocoria secondary to cataract.
can be visualized with an ophthalmoscope and are best seen with the pupil well dilated. The pathogenesis is unclear. In most cases, the opacities disappear spontaneously, often within a few weeks.

**Mendelian Inheritance**
Many cataracts unassociated with other diseases are hereditary. The most common mode of inheritance is autosomal dominant. Pene-

**Congenital Infection Syndrome**
Cataracts in infants and children can be a result of prenatal infection. Lens opacity may occur in any of the major congenital infection syndromes (e.g., toxoplasmosis, cytomegalovirus, syphilis, rubella, herpes simplex virus). Cataracts may also occur secondary to other perinatal infections, including measles, poliomyelitis, influenza, varicella-zoster, and vaccinia.

**Metabolic Disorders**
Cataracts are a prominent manifestation of many metabolic diseases, particularly certain disorders of carbohydrate, amino acid, calcium, and copper metabolism. A primary consideration in any infant with cataracts is the possibility of galactosemia (see Chapter 87.2). In classic infantile galactosemia, galactose-1-phosphate uridylyl transferase defi-

See Table 628-1 for a differential diagnosis of cataracts.

### Table 628-1  Differential Diagnosis of Cataracts

<table>
<thead>
<tr>
<th>DEVELOPMENTAL VARIANTS</th>
<th>GENETIC DISORDERS</th>
<th>MULTYSYSTEM GENETIC DISORDERS</th>
<th>MISCELLANEOUS DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity</td>
<td>Simple Mendelian Inheritance</td>
<td>Alport syndrome (hearing loss, renal disease)</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Mittendorf dot (remnant of hyaloid artery)</td>
<td>Autosomal dominant (most common)</td>
<td>Alström syndrome (nervous deafness, diabetes mellitus)</td>
<td>Drugs (corticosteroids)</td>
</tr>
<tr>
<td>Persistent pupillary membrane (remnant of embryonic lens vasculature)</td>
<td>Autosomal recessive</td>
<td>Aport disease (craniosynostosis, syndactyly)</td>
<td>Radiation</td>
</tr>
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<td></td>
<td>X-linked</td>
<td>Cockayne syndrome (premature senility, skin photosensitivity)</td>
<td>Trauma</td>
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<td></td>
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<td>Conrad syndrome (chondrodysplasia punctata)</td>
<td>Poliomyelitis</td>
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<td></td>
<td></td>
<td>Crouzon disease (dysostosis craniofacialis)</td>
<td>Infantile neuronal ceroid lipofuscinosis</td>
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<td></td>
<td></td>
<td>Ectodermal dysplasia</td>
<td>Rubella</td>
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<td></td>
<td></td>
<td>Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, and hypotrichosis)</td>
<td>Perinatal herpes simplex infection</td>
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<td></td>
<td></td>
<td>Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis)</td>
<td>Measles (rubella)</td>
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<td></td>
<td></td>
<td>Ichthyosis (keratinizing disorder with thick, scaly skin)</td>
<td>Poliomyelitis</td>
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<td></td>
<td></td>
<td>Incontinentia pigimt (dental anomalies, mental retardation, cutaneous lesions)</td>
<td>Influenza</td>
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<tr>
<td></td>
<td></td>
<td>Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease)</td>
<td>Varicella-zoster</td>
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<td></td>
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<td>Marfan syndrome</td>
<td>Ocular ANOMALIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meckel-Gruber syndrome (renal dysplasia, encephalocele)</td>
<td>Microphthalmia</td>
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<td></td>
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<td>Myotonic dystrophy</td>
<td>Coloboma</td>
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<td></td>
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<td>Nail–patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella)</td>
<td>Aniridia</td>
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<td></td>
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<td>Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia)</td>
<td>Mesodermal dysgenesis</td>
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<td></td>
<td>Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood)</td>
<td>Persistent pupillary membrane</td>
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<td>Peters anomaly (corneal opacifications with iris-corneal dysgenesis)</td>
<td>Posterior lenticular</td>
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<td></td>
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<td>Progeria</td>
<td>Persistent fetal vasculature</td>
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<td>Rieger syndrome (iris dysplasia, myotonic dystrophy)</td>
<td>Primitive hyaloid vascular system</td>
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<td>Rothmund-Thomson syndrome (poikiloderma: skin atrophy)</td>
<td>Retinitis pigmentosa</td>
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<td></td>
<td></td>
<td>Rubinstein-Taybi syndrome (broad great toe, mental retardation)</td>
<td>MISCELLANEOUS DISORDERS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation)</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sotos syndrome (cerebral gigantism)</td>
<td>Drugs (corticosteroids)</td>
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<tr>
<td></td>
<td></td>
<td>Spondyloepiphysial dysplasia (dwarfism, short trunk)</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Werner syndrome (premature aging in 2nd decade of life)</td>
<td>Trauma</td>
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</table>
Steroid-related cataracts characteristically are posterior subcapsular lens opacities. The incidence and severity vary. The relative significance of dose, mode of administration, duration of treatment, and individual susceptibility is controversial, and the pathogenesis of steroid-induced cataracts is unclear. The effect on vision depends on the extent and density of the opacity. In many cases, the acuity is only minimally or moderately impaired. Reversibility of steroid-induced cataracts may occur in some cases. All children receiving long-term steroid treatment should have periodic eye examinations.

Trauma to the eye is a major cause of cataracts in children (Fig. 628-3). Opacification of the lens may result from blunt or penetrating injury. Cataracts can be an important manifestation of child abuse. Cataract formation after exposure to radiation is dose and duration dependent. Adult research shows 50% occurrence in lens dose of 15 Gy. Delayed onset is the rule.

**Miscellaneous Disorders**

The list of multisystem syndromes and diseases associated with lens opacities and other eye anomalies is extensive (see Table 628-1).

**Treatment**

The treatment of cataracts that significantly interfere with vision includes the following: (1) surgical removal of lens material to provide an optically clear visual axis; (2) correction of the resultant aphakic refractive error with spectacles, contact lenses, or intraocular lens implantation; and (3) correction of any associated sensory deprivation amblyopia. Because the use of spectacles may not be possible in children after cataract removal, the use of contact lenses for visual rehabilitation is sometimes a medical necessity. Intraocular lens implantation has become a mainstay for visual rehabilitation in children 2 yr or older. A multicenter trial is underway to try to determine visual outcomes in very young children treated with a contact lens versus an intraocular lens implant. One yr after treatment, the children randomized into the intraocular lens implant group had more statistically significant intraoperative complications, adverse events, and need for additional intraocular surgery. Grating visual acuity at 1 yr was measured and 86% of patients in the contact lens group and 77% in the intraocular lens group had 20/200 vision or better. The median visual acuity between the groups was analyzed and although the median acuity was better in the contact lens group, the difference did not reach statistical significance. Final outcome will be the comparison of visual acuity at 4.5 yr of age. Treatment of the amblyopia may be the most demanding and difficult step in the visual rehabilitation of infants or children with cataracts. Not all cataracts require surgical intervention. Cataracts that are not visually significant should be monitored for change and the child should be monitored for development of amblyopia.

**Prognosis**

Prognosis depends on many factors, including the nature of the cataract, the underlying disease, age at onset, age at intervention, duration and severity of any attendant amblyopia, and presence of any associated ocular abnormalities (e.g., microphthalmia, retinal lesions, optic atrophy, glaucoma, nystagmus, and strabismus). Persistent amblyopia is the most common cause of poor visual recovery after cataract surgery in children. Secondary conditions and complications may develop in children who have had cataract surgery, including inflammatory sequelae, secondary membranes, glaucoma, retinal detachment, and changes in the axial length of the eye. All of these should be considered in planning treatment.
Abnormalities

Another form of heritable dislocation is ectopia lentis et pupillae temporally. The ectopia may be present at birth or may appear later in life. Another form of heritable dislocation is ectopia lentis. Simple ectopia lentis is usually transmitted as an autosomal dominant condition. The lens is generally displaced upward and temporally. The ectopia may be present at birth or may appear later in life. Another form of heritable dislocation is ectopia lentis et pupillae associated with systemic abnormalities is referred to as simple ectopia lentis. If the lens is displaced inferiorly and somewhat nasally. The subluxation of the lens occurs early in life and is often evident by 5 yr of age. In Weill-Marchesani syndrome, the displacement of the lens is often downward and forward, and the lens tends to be small and round.

Ectopia lentis is also associated occasionally with other conditions, including Ehlers-Danlos, Sturge-Weber, Crouzon, and Klippel-Feil syndromes; oxycephaly; and mandibulofacial dysostosis. A syndrome of dominantly inherited blepharoptosis, high myopia, and ectopia lentis has also been described.

Treatment and Prognosis

Displacement of the lens often results only in optical problems. In some cases, however, more serious complications may develop, such as glaucoma, uveitis, retinal detachment, or cataract. Management must be individualized according to the type of displacement, its cause, and the presence of any complicating ocular or systemic conditions. For many patients, optical correction by spectacles or contact lenses can be provided. Manipulation of the iris diaphragm with mydriatic or miotic drops may sometimes help improve vision. In selected cases, the best treatment is surgical removal of the lens. In many children, treatment of any associated amblyopia must be instituted early. In addition, for children with ectopia lentis, safety precautions should be taken to prevent injury to the eye.

Microspherophakia

The term microspherophakia refers to a small, round lens that may occur as an isolated anomaly (probably autosomal recessive) or in association with other ocular abnormalities, such as cataract, high myopia, or retinal detachment (possibly autosomal dominant). Microspherophakia may also occur in association with various systemic disorders, including Marfan syndrome, Weill-Marchesani syndrome, Alport syndrome, mandibulofacial dysostosis, and Klippel-Feil syndrome.

Anterior Lenticus

Anterior lenticus is a rare bilateral condition in which the anterior capsule of the lens thins, allowing the lens to bulge forward centrally. It may be accompanied by lens opacities or other eye anomalies and is a prominent feature of Alport syndrome. The increased curvature of the central area may cause high myopia. Spontaneous rupture of the anterior capsule may occur, requiring prompt surgical intervention.

Posterior Lenticus

Posterior lenticus, which occurs more commonly than anterior lenticonus, is characterized by a circumscribed round or oval bulge of the posterior lens capsule and cortex, involving the central region of the lens. In the early stages, by the red reflex test, this may look like an oil droplet. It occurs in infants and young children and tends to increase with age. Usually the lens material within and surrounding the capsular bulge eventually becomes opacified. Posterior lenticus usually occurs as an isolated ocular anomaly. It is generally unilateral but may be bilateral. It is believed to be sporadic, although autosomal dominant and X-linked inheritance has been suggested in some cases. Infants or children with posterior lenticus may require optical correction, amblyopia treatment, and surgery for progressive cataract.

Bibliography is available at Expert Consult.
Chapter 628  Abnormalities of the Lens

Bibliography

Uveitis in Childhood

Michelle M. Ariss, and Timothy P. Lindquist

The uveal tract (the inner vascular coat of the eye, consisting of the iris, ciliary body, and choroid) is subject to inflammatory involvement in a number of systemic diseases, both infectious and noninfectious, and in response to exogenous factors, including trauma and toxic agents (Table 629-1). Inflammation may affect any one portion of the uveal tract preferentially or all parts together.

**UVEITIS (IRITIS, CYCLITIS, CHORIORETINITIS)**

Inflammation may affect any portion of the uveal tract preferentially or all parts together. Inflammation of the anterior portion of the uvea (uveitis) is the most common form of uveitis; it is not associated with a particular cause, unlike inflammation involving the posterior portion of the uvea, which is more likely to be caused by infection or by another disease process. The uveal tract is preferentially involved in posterior uveitis (choroiditis) and in the iris (iridocyclitis).

**Table 629-1  Uveitis in Childhood**

<table>
<thead>
<tr>
<th>Anterior Uveitis</th>
<th>Posterior Uveitis (Chorioretinitis—May Involve Retina)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile idiopathic arthritis (pauciarticular)</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Toxocarasis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Parasites (toxocarasis)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Cat-scratch disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Crohn syndrome</td>
<td>Viral (rubella, herpes simplex, HIV, cytomegalovirus, West Nile)</td>
</tr>
<tr>
<td>Postinfecitious (enteric or genital) with arthritis and rash</td>
<td>Subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Spirochetal (syphilis, leptospiral)</td>
<td>Tubulointestinal nephritis and uveitis syndrome</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Anterior and/or posterior uveitis</td>
</tr>
<tr>
<td>Heterochromic iridocyclitis (Fuchs)</td>
<td>Sympathetic ophthalmia (trauma to other eye)</td>
</tr>
<tr>
<td>Viral (herpes simplex, herpes zoster)</td>
<td>Vogt-Koyanagi-Harada syndrome (uveotocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Behçet syndrome</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>Chronic infantile neurologic cutaneous arthritis syndrome (CINCA)</td>
<td>Subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Tubulointestinal nephritis and uveitis syndrome</td>
</tr>
<tr>
<td>Hyperimmunoglobulin D syndrome</td>
<td>Anterior and/or posterior uveitis</td>
</tr>
<tr>
<td>Tumor necrosis factor receptor–associated periodic syndrome</td>
<td>Sympathetic ophthalmia (trauma to other eye)</td>
</tr>
<tr>
<td>Muckle-Wells syndrome</td>
<td>Vogt-Koyanagi-Harada syndrome (uveotocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)</td>
</tr>
<tr>
<td>Hyperimmunoglobulin D syndrome</td>
<td>Behçet syndrome</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Lyme disease</td>
</tr>
</tbody>
</table>

**Figure 629-1  Cell and flare in the anterior chamber.** The flare represents protein leakage. (Courtesy of Peter Buch, CRA.)
**Figure 629-2** Focal atrophic and pigmented scars of chorioretinitis.

**Table 629-2** Examination Schedule for Children with JIA Without Known Iridocyclitis

<table>
<thead>
<tr>
<th>JIA SUBTYPE</th>
<th>AGE OF ONSET</th>
<th>≤6 yr</th>
<th>&gt;6 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OLIGOARTHRITIS OR POLYARTHRITIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive ANA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 4 yr duration</td>
<td></td>
<td>Every 3 mo</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>4-7 yr duration</td>
<td></td>
<td>Every 6 mo</td>
<td>Annually</td>
</tr>
<tr>
<td>More than 7 yr duration</td>
<td></td>
<td>Annually</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Negative ANA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 4 yr duration</td>
<td></td>
<td>Every 6 mo</td>
<td>Annually</td>
</tr>
<tr>
<td>4-7 yr duration</td>
<td></td>
<td>Annually</td>
<td>Annually</td>
</tr>
<tr>
<td>More than 7 yr duration</td>
<td></td>
<td>Annually</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annually regardless of duration</td>
<td>Annually regardless of duration</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis.

**Sympathetic ophthalmia** is a rare type of inflammatory response that affects the uninjured eye after a perforating injury. It may occur weeks, months, or even years after the injury. A hypersensitivity phenomenon is the most probable cause. Loss of vision in the uninjured (sympathizing) eye may result. Removal of the injured eye prevents the development of sympathetic ophthalmia but does not stop the progression of the disease once it has occurred. Therefore, early enucleation should be considered if there is no hope of visual recovery after a severe injury.

**Treatment**

The various forms of intraocular inflammation are treated according to their underlying systemic causal factors. When infection is proved or suspected, appropriate systemic antimicrobial or antiviral therapy is used. In some cases, intravitreal injection is indicated.

Elimination of the intraocular inflammation is important to reduce the risk of severe, and often permanent, vision loss. Untreated, the inflammatory process may lead to the development of band keratopathy (calcium deposition in the cornea), cataracts, glaucoma, and irreversible retinal damage. Anterior inflammation may respond well to topical corticosteroid treatment. Posterior cases often require systemic therapy. The use of topical and systemic corticosteroids can lead to the development of glaucoma and cataracts. To reduce the need for topical and systemic corticosteroids, systemic immunosuppression is often used in patients requiring long-term treatment. Commonly used immunosuppressive agents include methotrexate, cyclosporine, and tumor necrosis factor inhibitors. Multiple agents may be needed in recalcitrant cases. Cycloplegic agents, particularly atropine, are also used to reduce inflammation and to prevent adhesion of the iris to the lens (posterior synechiae), especially in anterior uveitis. Extensive posterior synechiae formation can lead to acute angle closure glaucoma.

Surgery may be required for patients who develop glaucoma because of the underlying disease process or the need for corticosteroid treatment. Cataract surgery should be delayed until the inflammation has been under control for a period of time. Cataract surgery in children with a history of prolonged uveitis can carry significant risk. There is no universal agreement concerning the use of intraocular lenses in these patients.

**Pars planitis** is an uncommon idiopathic form of intermediate uveitis characterized by anterior chamber involvement, anterior vitreous cells and condensations, and peripheral retinal vasculitis. The average age of onset is 9 yr. It is predominately bilateral and seen more frequently in males. Painless decreased vision is the usual presenting sign. The prognosis is good when adequate medical treatment is sought early in the course of the disease.

**Masquerade syndromes** can sometimes mimic intraocular inflammation. Retinoblastoma, leukemia, retained intraocular foreign body, juvenile xanthogranuloma, and peripheral retinal detachments may produce signs similar to those seen in uveitis. These syndromes should be kept in mind when evaluating a patient with suspected uveitis or if a patient does not respond as anticipated to antiinflammatory treatment.

*Bibliography is available at Expert Consult.*
Bibliography


Disorders of the Retina and Vitreous

Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in premature infants. It may be acute (early stages) or chronic (late stages). Clinical manifestations range from mild, usually transient changes of the peripheral retina to severe progressive vasoproliferation, scarring, and potentially blinding retinal detachment. ROP includes all stages of the disease and its sequelae. Retrolental fibroplasia, the previous name for this disease, described only the cicatricial stages.

Pathogenesis

Beginning at 16 wk of gestation, retinal angiogenesis normally proceeds from the optic disc to the periphery, reaching the outer rim of the retina (ora serrata) nasally at about 36 wk and extending temporally by approximately 40 wk. Injury to this process results in various pathologic and clinical changes. The first observation in the acute phase is cessation of vasculogenesis. Rather than a gradual transition...
from vascularized to avascular retina, there is an abrupt termination of the vessels, marked by a line in the retina. The line may then grow into a ridge composed of mesenchymal and endothelial cells. Cell division and differentiation may later resume, and vascularization of the retina may proceed. Alternatively, there may be progression to an abnormal proliferation of vessels out of the plane of the retina, into the vitreous, and over the surface of the retina. Cicatrization and traction on the retina may follow, leading to retinal detachment.

The risk factors associated with ROP are not fully known, but prematurity and the associated retinal immaturity at birth represent the major factors. Oxygenation, respiratory distress, apnea, bradycardia, heart disease, infection, hypercarbia, acidosis, anemia, and the need for transfusion are thought by some to be contributory factors. Generally, the lower the gestational age, the lower the birthweight, and the sicker the infant are, the greater the risk is for ROP.

The basic pathogenesis of ROP is still unknown. Exposure to the extraterine environment, including the necessarily high inspired oxygen concentrations, produces cellular damage, perhaps mediated by free radicals. Later in the course of the disease, peripheral hypoxia develops and vascular endothelial growth factors (VEGFs) are produced in the nonvascularized retina. These growth factors stimulate abnormal vasogenesis, and neovascularization may occur. Because of poor pulmonary function, a state of relative retinal hypoxia occurs. This causes upregulation of VEGF, which, in susceptible infants, can cause abnormal fibrovascular growth. This neovascularization may then lead to scarring and vision loss.

**Classification**

The currently used international classification of ROP describes the location, extent, and severity of the disease. To delineate location, the retina is divided into 3 concentric zones, centered on the optic disc (Fig. 630-1). Zone I, the posterior or inner zone, extends twice the disc-macular distance, or 30 degrees in all directions from the optic disc. Zone II, the middle zone, extends from the outer edge of zone I to the ora serrata nasally and to the anatomic equator temporally. Zone III, the outer zone, is the residual crescent that extends from the outer border of zone II to the ora serrata temporally. The extent of involvement is described by the number of circumferential clock hours involved.

The phases and severity of the disease process are classified into 5 stages. Stage 1 is characterized by a demarcation line that separates vascularized from avascular retina. This line lies within the plane of the retina and appears relatively flat and white. Often noted is abnormal branching or arcing of the retinal vessels that lead into the line. Stage 2 is characterized by a ridge; the demarcation line has grown, acquiring height, width, and volume and extending up and out of the plane of the retina. Stage 3 is characterized by the presence of a ridge and by the development of extraretinal fibrovascular tissue (Fig. 630-2A). Stage 4 is characterized by subtotal retinal detachment caused by traction from the proliferating tissue in the vitreous or on the retina. Stage 4 is subdivided into 2 phases: (a) subtotal retinal detachment not involving the macula and (b) subtotal retinal detachment involving the macula. Stage 5 is total retinal detachment.

When signs of posterior retinal vascular changes accompany the active stages of ROP, the term *plus disease* is used (see Fig. 630-2B and C). Patients reaching the point of dilatation and tortuosity of the retinal vessels also frequently demonstrate the associated findings of engorgement of the iris, pupillary rigidity, and vitreous haze.

**Clinical Manifestations and Prognosis**

In more than 90% of at-risk infants, the course is one of spontaneous arrest and regression, with little or no residual effects or visual disability. Fewer than 10% of infants have progression toward severe disease, with significant extraretinal vasoproliferation, cicatrization, detachment of the retina, and impairment of vision.

Some children with arrested or regressed ROP are left with demarcation lines, undervascularization of the peripheral retina, or abnormal branching, tortuosity, or straightening of the retinal vessels. Some are left with retinal pigmentary changes, dragging of the retina (so-called dragged disc), ectopia of the macula, retinal folds, or retinal breaks. Others proceed to total retinal detachment, which commonly assumes a funnel-like configuration. The clinical picture is often that of a retrolental membrane, producing leukokoria (a white reflex in the pupil). Some patients develop cataract, glaucoma, and signs of inflammation. The end stage is often a painful blind eye or a degenerated phthisical eye. The spectrum of ROP also includes myopia, which is often progressive and of significant degree in infancy. The incidence of anisometropia, strabismus, amblyopia, and nystagmus may also be increased.

**Diagnosis**

Systematic serial screening ophthalmologic examinations of infants at risk are recommended. Infants with a birthweight of less than 1,500 g or gestational age of 32 wk or less, and selected infants with a birthweight between 1,500 and 2,000 g or gestational age of more than 32 wk or selected infants with a birthweight of less than 2,000 g or gestational age of 32 wk or less, are recommended for screening. Infants with a birthweight between 1,500 and 2,000 g or gestational age of more than 32 wk or less, are recommended for screening.

---

**Figure 630-1** The retina is divided into 3 zones (A, diagram shows right eye) and the extent or severity of retinopathy in these zones is classified as stages (B). Stage 1 is characterized by a thin demarcation line between vascularized and nonvascularized retina, stage 2 by a ridge, stage 3 by extraretinal fibrovascular proliferation, stage 4 by partial retinal detachment, and stage 5 by total retinal detachment. In stage 3, extraretinal neovascularization can become severe enough to cause retinal detachment (stages 4-5), which usually leads to blindness. (B courtesy Lisa Hård. From Hellström A, Smith LEH, Dammann O: Retinopathy of prematurity. Lancet 382:1445-1454, 2013, Fig. 3, p. 1450.)
the treatment modality of choice. Peripheral retinal ablation should be considered for any eye with type 1 ROP. Serial examinations are indicated for any eye with type 2 ROP; treatment is considered if type 2 progresses to type 1 or if threshold ROP develops.

Clinical trials using systemic propranolol or intravitreal VEGF antagonists are ongoing and being evaluated for efficacy and risk.

### Prevention
Prevention of ROP ultimately depends on prevention of premature birth and its attendant problems (see Chapters 95 and 97.2). However, a number of other potential factors have been studied in order to decrease the occurrence of ROP in these premature infants. Ambient light had been considered by some to be a potential agent that could hopefully be manipulated. The LIGHT-ROP study definitively found that ambient light reduction had no impact on ROP. The association between ROP and oxygen saturation has been studied for decades. Recent research has focused on maintaining oxygen saturation levels for severely premature infants at levels sufficiently low to minimize the risk of ROP and sufficiently high to optimize survival.

### PERSISTENT FETAL VASCULATURE
Persistent fetal vasculature (PFV; formerly called persistent hyperplastic primary vitreous) includes a spectrum of manifestations caused by the persistence of various portions of the fetal hyaloid vascular system and associated fibrovascular tissue.

### Pathogenesis
During development of the eye, the hyaloid artery extends from the optic disc to the posterior aspect of the lens; it sends branches into the vitreous and ramifies to form the posterior portion of the vascular capsule of the lens. The posterior portion of the hyaloid system normally regresses by the 7th fetal mo and the anterior portion by the 8th fetal mo. Small remnants of the system, such as a tuft of tissue at the disc (Bergmeister papilla) or a tag of tissue on the posterior capsule of the lens (Mittendorf dot), are common findings in healthy persons. More extensive remnants and associated complications constitute PFV. Two major forms are described: anterior PFV and posterior PFV. Variability is great, and mixed or intermediate forms occur.

### Clinical Manifestations
The usual clinical feature of anterior PFV is the presence of a vascularized plaque of tissue on the back surface of the lens in an eye that is microphthalmic or slightly smaller than normal. The condition is usually unilateral and may occur in infants with no other abnormalities and no history of prematurity. The fibrovascular tissue tends to undergo gradual contraction. The ciliary processes become elongated, and the anterior chamber may become shallow. The lens usually is smaller than normal and may be clear but often becomes cataractous and may swell or absorb fluid. Large or anomalous vessels of the iris may be present.

32 wk with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk, should have retinal screening examinations. The timing of the initial screening exam is based on the infant’s age. Table 630-1 was developed from an evidence-based analysis of the Multicenter Trial of Cryotherapy for ROP. The examination can be stressful to fragile preterm infants, and the dilating drops can have untoward side effects. Infants must be carefully monitored during and after the examination. Some neonatologists and ophthalmologists advocate the use of topical tetracaine and/or oral sucrose to reduce the discomfort and stress to the infant. Follow-up is based on the initial findings and risk factors but is usually 2 wk or less.

### Treatment
In selected cases, cryotherapy or laser photocoagulation of the avascular retina reduces the more severe complications of progressive ROP. Advances in vitreoretinal surgical techniques have led to limited success in reattaching the retina in infants with total retinal detachment (stage 5 ROP), but the visual results are often disappointing. The Early Treatment for Retinopathy of Prematurity Cooperative study did find improved structural and visual outcomes with the redefined threshold for treatment. It demonstrated the importance of plus disease and the presence of posterior retinal involvement in the determination of when to treat ROP. This study also supported the fact that laser is

![Image of Retinopathy of Prematurity (ROP)](image)

Figure 630-2 Retinopathy of prematurity (ROP). A, In stage 3, there is a ridge and extraretinal vascular tissue. B, Retinal vessels are dilated and tortuous in active zone 1 ROP with plus disease. C, Zone 1 ROP with plus disease.
The anterior chamber angle may have abnormalities. In time, the cornea may become cloudy.

Anterior PFV is usually noted in the 1st wk or mo of life. The most frequent presenting signs are leukocoria (white pupillary reflex), strabismus, and nystagmus. The course is usually progressive and the outcome poor. Major complications are spontaneous intraocular hemorrhage, swelling of the lens caused by rupture of the posterior capsule, and glaucoma. The eye may eventually deteriorate. The spectrum of posterior PFV includes fibroglial veils around the disc and macula, vitreous membranes and stalks containing hyaloid artery remnants projecting from the disc, and meridional retinal folds. Traction detachment of the retina may occur. Vision may be impaired, but the eye is usually retained.

### Treatment

Surgery is performed in an effort to prevent complications, to preserve the eye and a reasonably good cosmetic appearance, and, in some cases, to salvage vision. Surgical treatment usually involves aspirating the lens and excising the abnormal tissue. If useful vision is to be attained, refractive correction and aggressive amblyopia therapy are required. In some cases, the affected eye is enucleated because distinguishing between this white mass and retinoblastoma can be difficult. Ultrasonography and CT are valuable diagnostic aids.

### RETINOBLASTOMA

Also see Chapter 502.

Retinoblastoma (Fig. 630-3) is the most common primary malignant intraocular tumor of childhood. It occurs in approximately 1/15,000 live births; 250-300 new cases are diagnosed in the United States annually. Hereditary and nonhereditary patterns of transmission occur; there is no gender or race predilection. The hereditary form occurs earlier and is usually bilateral and multifocal, whereas the non-hereditary form is generally unilateral and unifocal. Fifteen percent of unilateral cases are hereditary. Bilateral cases often present earlier than unilateral cases. Unilateral tumors are often large by the time they are discovered. The average age at diagnosis is 15 mo for bilateral cases, compared with 27 mo for unilateral cases. It is unusual for a child to present with a retinoblastoma after 3 yr of age. Rarely, the tumor is discovered at birth, during adolescence, or even in early adulthood.

#### Clinical Manifestations

The clinical manifestations of retinoblastoma vary, depending on the stage at which the tumor is detected. The initial sign in the majority of patients is a white pupillary reflex (leukocoria). Leukocoria results because of the reflection of light off the white tumor. The second most frequent initial sign of retinoblastoma is strabismus. Less-frequent presenting signs include pseudohypopyon (tumor cells layered inferiorly in front of the iris) caused by tumor seeding in the anterior chamber of the eye, hyphema (blood layered in front of the iris) secondary to iris neovascularization, vitreous hemorrhage, and signs of orbital cellulitis. On examination, the tumor appears as a white mass, sometimes small and relatively flat, sometimes large and protuberant. It may appear nodular. Vitreous haze or tumor seeding may be evident.

The retinoblastoma gene is a recessive suppressor gene located on chromosome 13 at the 13q14 region. Because of the hereditary nature of retinoblastoma, family members of affected children should undergo

![Figure 630-3 Progression of retinoblastoma from small intraretinal tumors to massive orbital retinoblastoma probably extending into the brain. Progression of retinoblastoma (A) from small intraretinal tumors that can be cured by laser treatment and cryotherapy (TNM T1a, IIRC A) to massive orbital retinoblastoma probably extending into the brain (TNM T4a-b). A difference in age at diagnosis recorded between Canada and Kenya could be the difference between possible cure and certain death (B). The Canadian child with leukocoria was diagnosed because of the left-hand image, which was taken by his sister with his mother’s mobile phone. IIRC, International Intraocular Retinoblastoma Classification; TNM, Tumor Node Metastasis Cancer Staging. (From Dimaras H, Kimani K, Dimba EAO, et al: Retinoblastoma. Lancet 379:1436-1444, 2012, Fig. 1, p. 1438.)](image-url)
a complete ophthalmologic examination and genetic counseling. Newborn siblings and children of affected patients should be referred to an ophthalmologist shortly after birth, when the peripheral retina can be evaluated without the need for an examination under anesthesia.

**Diagnosis**
This is made by direct observation by an experienced ophthalmologist. Ancillary testing such as CT or ultrasonography may help to confirm the diagnosis and demonstrate calcification within the mass. MRI may better detect the presence of an associated pineoblastoma (trilateral retinoblastoma). A definitive diagnosis occasionally cannot be made, and removal of the eye must be considered to avoid the possibility of lethal metastasis of the tumor. Because a biopsy can lead to spread of the tumor, histologic confirmation before enucleation is not possible in most cases. Therefore, removal of a blind eye in which the diagnosis of retinoblastoma is likely may be appropriate.

**Treatment**
Therapy varies, depending on the size and location of the tumor as well as whether it is unilateral or bilateral. Advanced tumors may be treated by enucleation. Other treatment modalities include the use of external beam irradiation, radiation plaque therapy, laser or cryotherapy, and chemotherapy. During the last decade there has been a dramatic shift in the treatment of retinoblastomas. Chemoreduction (systemic chemotherapy) followed by local therapies (i.e., laser therapy, cryotherapy, and brachytherapy) has markedly reduced the use of external beam radiation and is a more vision-sparing technique. Those children who are irradiated during their 1st yr of life are 2-8 times more likely to develop second cancers than those irradiated after 1 yr of age. Patients treated with radiation tend to develop brain tumors and sarcomas of the head and neck. Secondary cataracts can also develop from radiation.

Nonocular secondary tumors are common in patients with germinal mutations estimated to occur with an incidence of 1% per yr of life. The most common secondary tumor is osteogenic sarcoma of the skull and long bones; the risk is higher in patients treated with radiation. Other malignancies include lung, brain, soft tissue, and skin.

The prognosis for children with retinoblastoma depends on the size and extension of the tumor. When confined to the eye, most tumors can be cured. The prognosis for long-term survival is poor when the tumor has extended into the orbit or along the optic nerve.

**RETINITIS PIGMENTOSA**
This progressive retinal degeneration is characterized by pigmentary changes, arteriolar attenuation, usually some degree of optic atrophy, and progressive impairment of visual function. Dispersion and aggre- gation of the retinal pigment produce various ophthalmoscopically visible changes, ranging from granularity or motting of the retinal pigment pattern to distinctive focal pigment aggregates with the configuration of bone spicules (Fig. 630-4). Other ocular findings include subcapsular cataract, glaucoma, and keratoconus.

Impairment of night vision or dark adaptation is often the first clinical manifestation. Progressive loss of peripheral vision, often in the form of an expanding ring scotoma or concentric contraction of the field, is usual. There may be loss of central vision. Retinal function, as measured by electoretinography (ERG), is characteristically reduced. The disorder may be autosomal recessive, autosomal dominant, or X linked. Children with autosomal recessive retinitis pigmentosa are more likely to become symptomatic at an earlier age (median age 10.7 yr). Those with autosomal dominant retinitis pigmentosa are more likely to present in their 20s. Only supportive treatment is available.

A special form of retinitis pigmentosa is *Leber congenital retinal amaurosis*, in which the retinal changes tend to be pleomorphic, with various degrees of pigment disorder, arteriolar attenuation, and optic atrophy. The retina may appear normal during infancy. Vision impairment, nystagmus, and poor pupillary reaction are usually evident soon after birth, and the ERG findings are abnormal early and confirm the diagnosis. Retinal pigment epithelium–specific 65-kDa deficiency is the cause of autosomal recessive disease. Gene replacement therapy (subretinal injection) presently shows early promise for people affected with Leber congenital retinal amaurosis.

**Usher syndrome**, an autosomal recessive disorder, is the most common cause of retinitis pigmentosa and sensorineural deafness (incidence 1:25,000). Type 1 Usher syndrome presents at birth with profound hearing loss and poor balance; visual loss progresses more slowly and begins during adolescence. Patients with type 3 disease have normal hearing at birth but develop hearing loss and night blindness around puberty. To date, 11 genetic loci have been located (5 for type 1; 3 for type 2; 1 for type 3).

Clinically similar, secondary pigmentary retinal degenerations that need to be differentiated from retinitis pigmentosa occur in a wide variety of metabolic diseases, neurodegenerative processes, and multifaceted syndromes. Examples include the progressive retinal changes of the mucopolysaccharidoses (particularly Hurler, Hunter, Scheie, and Sanfilippo syndromes; see Chapter 88) and certain of the late-onset gangliosidoses (Batten-Mayou, Spielmeyer-Vogt, and Jansky-Bielschowsky diseases; see Chapters 86.4 and 599.2), the progressive retinal degeneration that is associated with progressive external ophthalmoplegia (Kearns-Sayre syndrome; see Chapter 598.2), and the retinitis pigmentosa–like changes in the Laurence-Moon and Bardet-Biedl syndromes. The retinal manifestations of abetalipoproteinemia (Bassen-Kornzweig syndrome; see Chapter 86) and Refsum disease (see Chapter 86.2) are also similar to those found in retinitis pigmentosa. The diagnosis of these latter two disorders in a patient with presumed retinitis pigmentosa is important because treatment is possible. There is also an association of retinitis pigmentosa and congenital hearing loss, as in Usher syndrome.

**STARGARDT DISEASE (FUNDUS FLAVIMACULATUS)**
This autosomal recessive retinal disorder is characterized by slowly progressive bilateral macular degeneration and vision impairment. It usually appears at 8-14 yr of age, and affected children are often initially misdiagnosed as having functional visual loss. The foveal reflex becomes obtunded or appears grayish, pigment spots develop in the macular area, and macular depigmentation and chorioretinal atrophy eventually occur. Macular hemorrhages also may develop. Some patients also have white or yellow spots beyond the macula or pigmentary changes in the periphery; the term *fundus flavimaculatus* is commonly used for this condition. It is now recognized that Stargardt disease and fundus flavimaculatus represent different entities on the spectrum of the same disease. Central visual acuity is reduced, often to 20/200, but total loss of vision does not occur. ERG findings vary. The condition is not associated with central nervous system abnormalities and is to be
differentiated from the macular changes of many progressive metabolic neurodegenerative diseases. The genetic mutation responsible for Stark-gardt macular dystrophy has been identified.

**BEST VITELLIFORM DEGENERATION**
This macular dystrophy is characterized by a distinctive yellow or orange discoid subretinal lesion in the macula, resembling the intact yolk of a fried egg. Diagnosis is usually made at 3-15 yr of age with a mean age of presentation of 6 yr. Vision is usually normal at this stage. The condition may be progressive; the yolk-like lesion may eventually degenerate (“scramble”) and result in pigmentation, chorioretinal atrophy, and vision impairment. The condition is usually bilateral. There is no association with systemic abnormalities. Inheritance is usually autosomal dominant. The vitelliform macular dystrophy gene (VMD2) has been identified and DNA testing is available. In vitelliform macular degeneration, the ERG response is normal. Electrooculographic findings are abnormal in affected patients and carriers, and this test is useful in diagnosis and in genetic counseling.

**CHERRY-RED SPOT**
Because of the special histologic features of the macula, certain pathologic processes affecting the retina produce an ophthalmoscopically visible sign referred to as a cherry-red spot, a bright to dull red spot at the center of the macula and accentuated by a grayish-white or yellowish halo (Fig. 630-5). The halo is a result of a loss of transparency of the retinal ganglion cell layer secondary to edema or lipid accumulation, or both. Because ganglion cells are not present in the fovea, the retina surrounding the fovea is opacified but the fovea transmits the normal underlying choroidal color (red), accounting for the presence of the cherry-red spot. A cherry-red spot typically occurs in certain sphingolipidoses, principally in Tay-Sachs disease (GM_1 type 1), in the Sandhoff variant (GM_1 type 2), and in generalized gangliosidosis (GM_1 type 1). Similar but less distinctive macular changes occur in some cases of metachromatic leukodystrophy (sulfatide lipidosis), in some forms of neuronopathic Niemann-Pick disease, galactosialidosis, and in certain mucolipidoses. The cherry-red spot that characteristically occurs as a result of retinal ischemia secondary to vasospasm, ocular contusion, or occlusion of the central retinal artery must be differentiated from the cherry-red spot of neurodegenerative disease (see Chapters 86.4 and 599).

**PHAKOMAS**
See also Chapter 596.

These are the herald lesions of the hamartomatous disorders. In Bourneville disease (tuberous sclerosis), the distinctive ocular lesion is a refractile, yellowish, multinodular cystic lesion arising from the disc or retina; the appearance of this typical lesion is often compared with that of an unripe mulberry (Fig. 630-6). Equally characteristic and more common in tuberous sclerosis are flatter, yellow to whitish retinal lesions, varying in size from minute dots to large lesions approaching the size of the disc. These lesions are benign astrocytic proliferations. Rarely, similar retinal phakomas occur in von Recklinghausen disease (neurofibromatosis). In von Hippel-Lindau disease (angiomatosis of the retina and cerebellum), the distinctive fundus lesion is a hemangioblastoma; this vascular lesion usually appears as a reddish globular mass with large paired arteries and veins passing to and from the lesion. In Sturge-Weber syndrome (encephalofacial angiomatosis), the fundus abnormality is a choroidal hemangioma; the hemangioma may impart a dark color to the affected area of the fundus, but the lesion is best seen with fluorescein angiography.

**RETNOSCHISIS**
Congenital hereditary retinoschisis, also referred to as juvenile X-linked retinoschisis, is a bilateral vitreoretinal dystrophy that has a bimodal age of presentation. The first group presents with strabismus and nystagmus at a mean age of 1.5-2 yr and is the most severely affected group. The second group presents at 6-7 yr with poor vision. It is characterized by splitting of the retina into inner and outer layers. The usual ophthalmoscopically finding in affected males is an elevation of the inner layer of the retina, most commonly in the inferotemporal quadrant of the fundus, often with round or oval holes visible in the inner layer. Schisis of the fovea is virtually pathognomonic and is found in almost 100% of patients. Ophthalmoscopically, this appears in early stages as small, fine striae in the internal limiting membrane. These striae radiate outward in a petaloid or spoke wheel configuration. In some cases, frank retinal detachment or vitreous hemorrhage occurs. Vision impairment varies from mild to severe; visual acuity may worsen with age, but good vision is often retained. Carrier females are asymptomatic, but linkage studies may be useful to help detect carriers.

**RETNAL DETACHMENT**
A retinal detachment is a separation of the outer layers of the retina from the underlying retinal pigment epithelium (RPE). During embryogenesis, the retina and RPE are initially separated. During ocular development, they join together and are held in apposition to each other by various physiologic mechanisms. Pathologic events leading to a retinal detachment return the retina–RPE to its former separated state. The detachment can occur as a congenital anomaly but more commonly arises secondary to other ocular abnormalities or trauma. Three types of detachment are described; each may occur in children. Rhegmatogenous detachments result from a break in the
helpful.

Exudative vitreoretinopathy (FEVR) is usually an autosomal dominant condition with incomplete penetrance. Asymptomatic family members often display a zone of avascular peripheral retina.

The findings in FEVR may resemble those of ROP in the cicatricial stages, but unlike ROP, the neovascularization of FEVR seems to develop years after birth and most patients with FEVR have no history of prematurity, oxygen therapy, prenatal or postnatal injury or infection, or developmental abnormalities. FEVR is also to be differentiated from Coats disease, angiomatosis of the retina, peripheral uveitis, and other disorders of the posterior segment.

COATS DISEASE

This exudative retinopathy of unknown cause is characterized by telangiectasia of retinal vessels with leakage of plasma to form intraretinal and subretinal exudates and by retinal hemorrhages and detachment (Fig. 630-7). The condition is usually unilateral. It predominantly affects boys, usually appearing in the 1st decade. The condition is nonfamilial and for the most part occurs in otherwise healthy children. The most frequent presenting signs are blurring of vision, secondary strabismus or nystagmus, or leukocoria (white pupillary reflex). In addition to direct examination of the eye, special diagnostic studies such as ultrasonography and neuroimaging (CT, MRI) may be necessary to establish the cause of the detachment and the appropriate treatment. Prompt treatment is essential if vision is to be salvaged.

FAMILIAL EXUDATIVE VITREORETINOPATHY

This progressive retinal vascular disorder is of unknown cause, but clinical and angiographic findings suggest an aberration of vascular development. Avascularity of the peripheral temporal retina is a significant finding in most cases, with abrupt cessation of the retinal capillary network in the region of the equator. The avascular zone often has a wedge- or V-shaped pattern in the temporal meridian. Glial proliferation or well-marked retinochoroidal atrophy may be found in the avascular zone. Excessive branching of retinal arteries and veins, dilation of the capillaries, arteriovenous shunt formation, neovascularization, and leakage from retinal vessels of the farthest vascularized retina occur. Vitreoretinal adhesions are usually present at the peripheral margin of the vascularized retina. Traction, retinal dragging and temporal displacement of the macula, falciform retinal folds, and retinal detachment are common. Intraretinal or subretinal exudation, retinal hemorrhage, and recurrent vitreous hemorrhages may develop. Patients may also develop cataracts and glaucoma. Vision impairment of varying severity occurs. The condition is usually bilateral. Familial exudative vitreoretinopathy (FEVR) is usually an autosomal dominant condition with incomplete penetrance. Asymptomatic family members often display a zone of avascular peripheral retina.

The findings in FEVR may resemble those of ROP in the cicatricial stages, but unlike ROP, the neovascularization of FEVR seems to develop years after birth and most patients with FEVR have no history of prematurity, oxygen therapy, prenatal or postnatal injury or infection, or developmental abnormalities. FEVR is also to be differentiated from Coats disease, angiomatosis of the retina, peripheral uveitis, and other disorders of the posterior segment.

HYPERTENSIVE RETINOPATHY

In the early stages of hypertension, no retinal changes may be observable. Generalized constriction and irregular narrowing of the arterioles are usually the first signs in the fundus. Other alterations include retinal edema, flame-shaped hemorrhages, cotton-wool spots (retinal nerve fiber layer infarcts), and papilledema (Fig. 630-8). These changes are reversible if the hypertension can be controlled in the early stages, but in long-standing hypertension, irreversible changes may occur. Thickening of the vessel wall may produce a silver- or copper-wire appearance. Hypertensive retinal changes in a child should alert the physician to renal disease, pheochromocytoma, collagen disease, and cardiovascular disorders, particularly coarctation of the aorta.

DIABETIC RETINOPATHY

The retinal changes of diabetes mellitus are classified as nonproliferative or proliferative. Nonproliferative diabetic retinopathy is characterized by retinal microaneurysms, venous dilation, retinal hemorrhages, and exudates. The microaneurysms appear as tiny red dots. The hemorrhages may be of both the dot and blot type, representing deep intraretinal bleeding, and the splinter or flame-shaped type, involving the superficial nerve fiber layer. The exudates tend to be deep and to appear waxy. There may also be superficial nerve fiber infarcts called cytoid bodies or cotton-wool spots, as well as retinal edema. These signs may wax and wane. They are seen primarily in the posterior pole, around the disc and macula, well within the range of direct ophthalmoscopy. Involvement of the macula may lead to decreased vision.

Proliferative retinopathy, the more serious form, is characterized by neovascularization and proliferation of fibrovascular tissue on the retina, extending into the vitreous. Neovascularization may occur on the optic disc, elsewhere on the retina, or on the iris and in the anterior chamber angle (or rubeosis irides) (Fig. 630-9). Traction on these new vessels leads to hemorrhage and, eventually, scarring. The vision-threatening complications of proliferative diabetic retinopathy are retinal and vitreous hemorrhages, cataract formation, traction, and retinal detachment. Neovascularization of the iris may lead to secondary glaucoma if not treated promptly.
Diabetic retinopathy involves the alteration and nonperfusion of retinal capillaries, retinal ischemia, and neovascularization, but its pathogenesis is not yet completely understood, either in terms of location of the primary pathogenetic mechanism (retinal vessels vs surrounding neuronal or glial tissue) or the specific biochemical factors involved. The better the degree of long-term metabolic control, the lower the risk of diabetic retinopathy.

Clinically, the prevalence and course of retinopathy relate to a patient's age and to disease duration. Detectable microvascular changes are rare in prepubertal children, with the prevalence of retinopathy increasing significantly after puberty, especially after the age of 15 yr. The incidence of retinopathy is low during the 1st 5 yr of disease and increases progressively thereafter, with the incidence of proliferative retinopathy becoming substantial after 10 yr and with increased risk of visual impairment after 15 yr or more.

Ophthalmic examination guidelines have been proposed by the American Academy of Pediatrics. An initial exam is recommended at age 9 yr if the diabetes is poorly controlled. If the diabetes is well controlled, an initial exam 3 yr after puberty with annual follow-up is recommended.

In addition to retinopathy, patients with juvenile-onset diabetes may develop optic neuropathy, characterized by swelling of the disc and blurring of vision. Patients with diabetes may also develop cataracts, even at an early age, sometimes with rapid progression.

**Treatment**

Macular edema is the leading cause of visual loss in diabetic persons. Photocoagulation may be used to decrease the risk of continued vision loss in patients with macular edema.

Proliferative retinopathy causes the most severe vision loss and can lead to total loss of vision and even loss of the eye. Patients who have proliferative disease and who display certain high-risk characteristics should undergo panretinal photocoagulation to preserve their central vision. Neovascularization of the iris is also treated with panretinal photocoagulation to stop the development of neovascular glaucoma.

Vitrectomy and other intracocular surgery may be necessary in patients with nonresolving vitreous hemorrhage or traction retinal detachment. The value of technologic advances, such as insulin infusion pumps and pancreatic transplants, in preventing ocular complications is under investigation (see Chapter 589).

**SUBACUTE BACTERIAL ENDOCARDITIS**

At some time during the course of the disease, retinopathy is present in approximately 40% of cases of subacute bacterial endocarditis. The lesions include hemorrhages, hemorrhages with white centers (Roth spots), papilledema, and, rarely, embolic occlusion of the central retinal artery.

**BLOOD DISORDERS**

In primary and secondary anemias, retinopathy in the form of hemorrhages and cotton-wool patches may occur. Vision can be affected if hemorrhage occurs in the macular area. The hemorrhages may be light and feathery or dense and preretinal. In polycythemia vera, the retinal veins are dark, dilated, and tortuous. Retinal hemorrhages, retinal edema, and papilledema may be observed. In leukemia, the veins are characteristically dilated, with sausage-shaped constrictions; hemorrhages, particularly white-centered hemorrhages and exudates, are common during the acute stage. In the sickling disorders, fundus changes include vascular tortuosity, arterial and venous occlusions, “salmon patches,” refractile deposits, pigmented lesions, arteriolar-venous anastomoses, and neovascularization (with “sea-fan” formations), sometimes leading to vitreous hemorrhage and retinal detachment. Individuals with sickle cell hemoglobin C and sickle cell hemoglobin β-thalassemia hemoglobinopathies are at a higher risk of the development of retinopathy than are those with homozygous hemoglobin S disease. It is thought that the more anemic state of those patients with homozygous hemoglobin S disease offers protection from vascular occlusions in the retina.

**TRAUMA-RELATED RETINOPATHY**

Retinal changes may occur in patients who suffer trauma to other parts of the body. The occurrence of retinal hemorrhages in infants who have been physically abused is well documented (Fig. 630-10; see Chapter 40). Retinal, subretinal, subhyaloid, and vitreous hemorrhages have been described in infants and young children with inflicted neurotrauma. Often there are no signs of direct trauma to the eye, pericentral region, or head. Such cases may result from violent shaking of an infant, and permanent retinal damage may result.

In patients with severe head or chest compressive trauma, a traumatic retinal angiopathy known as *Purtscher retinopathy* may occur. This is characterized by retinal hemorrhage, cotton-wool spots, possible disc swelling, and decreased vision. The pathogenesis is unclear, but there is evidence of arteriolar obstruction in this condition. A Purtscher-like fundus picture may also occur in several nontraumatic settings, such as acute pancreatitis, lupus erythematosus, and childbirth.

**MYELINATED NERVE FIBERS**

Myelination of the optic nerve fibers normally terminates at the level of the disc, but in some individuals, ectopic myelination extends to nerve fibers of the retina. The condition is most commonly seen adjacent to the disc, although more peripheral areas of the retina may be
involved. The characteristic ophthalmoscopic picture is a focal white patch with a feathered edge or brushstroke appearance. Because the macula is generally unaffected, the visual prognosis is good. A relative or absolute visual field defect corresponding to areas of ectopic myelination is usually the only associated ocular abnormality. Extensive unilateral involvement, however, is associated with ipsilateral myopia, amblyopia, and strabismus. If unilateral high myopia and amblyopia are present, appropriate optical correction and occlusion therapy should be instituted. For unknown reasons, the disorder is more commonly encountered in patients with craniofacial dysostosis, oxycephaly, neurofibromatosis, and Down syndrome.

**COLOBOMA OF THE FUNDUS**

The term *coloboma* describes a defect such as a gap, notch, fissure, or hole. The typical fundus coloboma is a result of malclosure of the embryonic fissure, which leaves a gap in the retina, RPE, and choroid, thus baring the underlying sclera. The defect may be extensive, involving the optic nerve, ciliary body, and iris and even the lens, or it may be localized to 1 or more portions of the fissure. The usual appearance is of a well-circumscribed, wedge-shaped white area extending inferonasally below the disc, sometimes involving or engulfing the disc. In some cases, there is ectasia or cyst formation in the area of the defect. Less-extensive colobomatous defects may appear as only single or multiple focal punched-out chorioretinal defects or anomalous pigmentation of the fundus in the line of the embryonic fissure. Colobomas may occur in 1 or both eyes. A visual field defect usually corresponds to the chorioretinal defect. Visual acuity may be impaired, particularly if the defect involves the disc or macula.

Fundus colobomas may occur in isolation as sporadic defects or as an inherited condition. Isolated colobomatous anomalies are commonly inherited in an autosomal dominant manner with highly variable penetrance and expressivity. Family members of affected patients should receive appropriate genetic counseling. Colobomas may also be associated with such abnormalities as microphthalmia, glioneuroma of the eye, cyclopia, or encephalocele. They occur in children with various chromosomal disorders, including trisomies 13 and 18, triploidy, cat's-eye syndrome, and 4p−. Ocular colobomas also occur in many multisystem disorders, including the CHARGE (C, coloboma; H, heart disease; A, atresia choanae; R, retarded growth and development and/or central nervous system anomalies; G, genetic anomalies and/or hypogonadism; E, ear anomalies and/or deafness) association; Joubert, Aicardi, Meckel, Warburg, and Rubinstein-Taybi syndromes; linear sebaceous nevus; Goldenhar and Lenz microphthalmia syndromes; and Goltz focal dermal hypoplasia.

*Bibliography is available at Expert Consult.*
Bibliography
OPTIC NERVE HYPOPLASIA

Hypoplasia of the optic nerve is a nonprogressive condition characterized by a subnormal number of optic nerve axons with normal mesodermal elements and glial supporting tissue. In typical cases, the nerve head is small and pale, with a pale or pigmented peripapillary halo or double-ring sign.

This anomaly is associated with defects of vision and of visual fields of varying severity, ranging from blindness to normal or near-normal vision. It may be associated with systemic anomalies that most commonly involve the central nervous system (CNS). Protean CNS defects such as hydranencephaly or anencephaly or more focal lesions compatible with continued development of a patient may accompany optic nerve hypoplasia, but unilateral or bilateral optic nerve hypoplasia may be found without any concomitant defects.

Optic nerve hypoplasia is a principal feature of septooptic dysplasia of de Morsier, a developmental disorder characterized by the association of anomalies of the midline structures of the brain with hypoplasia of the optic nerves, optic chiasm, and optic tracts; typically noted are agenesis of the septum pellucidum, partial or complete agenesis of the corpus callosum, and malformation of the fornix, with a large chiasmatic cistern. Patients may have hypothalamic abnormalities and endocrine defects, ranging from panhypopituitarism to isolated deficiency of growth hormone, hypothyroidism, or diabetes insipidus.

Neonatal hypoglycemia and seizures are important presenting signs in affected infants.

MRIs are preferred for evaluating CNS abnormalities in patients with optic nerve hypoplasia. During MRI, special attention should be directed to the pituitary infundibulum, where ectopia of the posterior pituitary may be found. Posterior pituitary ectopia appears on MRI as an absence of the pituitary infundibulum with an abnormal bright spot at the upper infundibulum area. This abnormality is present in approximately 15% of patients and suggests posterior pituitary hormone deficiency, requiring further endocrinologic work-up. Endocrine function should be watched closely in patients with optic nerve hypoplasia. The cause of optic nerve hypoplasia remains unclear.

Children with periventricular leukomalacia display an unusual form of optic nerve hypoplasia. The optic nerves demonstrate a large cup within a normal-size optic disc. This form of optic nerve hypoplasia occurs secondary to transsynaptic degeneration of optic axons caused by the primary bilateral lesion in the optic radiation (periventricular leukomalacia).

OPTIC NERVE COLOBOMA

Optic nerve colobomas can be unilateral or bilateral. The visual acuity can range from normal to complete blindness. The coloboma develops secondary to incomplete closure of the embryonic fissure. The defect may produce a partial or total excavation of the optic disc (Fig. 631-1).
Chorioretinal and iris colobomas may also occur. Optic nerve colobomas may be seen in a multitude of ocular and systemic abnormalities including the CHARGE (C, coloboma; H, heart disease; A, atresia choanae; R, retarded growth and development and/or CNS anomalies; G, genetic anomalies and/or hypogonadism; E, ear anomalies and/or deafness) association.

**MORNING GLORY DISC ANOMALY**

This term describes a congenital malformation of the optic nerve characterized by an enlarged, excavated, funnel-shaped disc with an elevated rim, resembling a morning glory flower. White gial tissue is present in the central part of the disc. The retinal vessels are abnormal and appear at the peripheral disc and course over the elevated pink rim in a radial fashion. Pigmentary mottling of the peripapillary region is usually seen. Most cases are unilateral. Females are affected twice as often as males. Visual acuity is usually severely reduced. Morning glory disc anomaly has been associated with basal encephalocoele in patients with midfacial anomalies. Abnormalities of the carotid circulation can also be seen in patients with morning glory anomaly. Moyamoya disease is a well-described associated finding.

**TILTED DISC**

In this congenital anomaly, the vertical axis of the optic disc is directed obliquely, so that the upper temporal portion of the nerve head is more prominent and anterior to the lower nasal portion of the disc. The retinal vessels emerge from the upper temporal portion of the disc rather than from the nasal side. Often noted is a peripapillary crescent or conus. Associated visual field defects and myopic astigmatism may be found. Clinical recognition of the tilted disc syndrome is important to avoid confusion of its disc and visual field signs with those of papilledema and intracranial tumor.

**DRUSEN OF THE OPTIC NERVE**

These globular, acellular bodies are thought to arise from axoplasmic derivatives of disintegrating nerve fibers. Drusen may be buried within the optic nerve, producing elevation of the optic nerve head (which can be confused with papilledema), or they may be partially or completely exposed, appearing as refractile bodies at the surface of the disc. Visual field defects and spontaneous peripapillary nerve fiber layer hemmorhages may occur in association with drusen. Drusen may occur as an autosomal dominant condition. B scan ultrasonography can help positively identify drusen suspected on clinical ophthalmic exam (Fig. 631-2).

**PAPILLEDEMA**

The term papilledema is reserved to describe swelling of the nerve head secondary to increased intracranial pressure (ICP). Clinical manifestations of papilledema include edematous blurring of the disc margins, fullness or elevation of the nerve head, partial or complete obliteration of the disc cup, capillary congestion and hyperemia of the nerve head, generalized engorgement of the veins, loss of spontaneous venous pulsation, nerve fiber layer hemorrhages around the disc, and peripapillary exudates (see Fig. 590-1 in Chapter 590). In some cases, edema extending into the macula may produce a fan- or star-shaped figure. In addition, concentric peripapillary retinal wrinkling (Paton lines) may be noted. Transient obstruction of vision may occur, lasting seconds and associated with postural changes. Vision, however, is usually normal in acute papilledema. Normally, when the ICP is relieved, the papilledema resolves and the disc returns to a normal or nearly normal appearance within 6-8 wk. Sustained chronic papilledema or long-standing unrelied increased ICP may, however, lead to permanent nerve fiber damage, astroplastic changes of the disc, macular scarring, and impairment of vision.

The pathophysiology of papilledema is probably as follows: elevation of intracranial subarachnoid cerebrospinal fluid (CSF) pressure, elevation of CSF pressure in the sheath of the optic nerve, elevation of tissue pressure in the optic nerve, stasis of axoplasmic flow and swelling of the nerve fibers in the optic nerve head, and secondary vascular changes and the characteristic ophthalmoscopic signs of venous stasis. Associated neuroophthalmic signs of increased ICP in infants and children include 6th cranial nerve palsy and attendant esotropia, lid retraction, paresis of upward gaze, tonic downward deviation of the eyes, and convergent nystagmus.

The common etiologies of papilledema in childhood are intracranial tumors and obstructive hydrocephalus, intracranial hemorrhage, the cerebral edema of trauma, meningencephalitis, toxic encephalopathy, and certain metabolic diseases. Whatever the cause, the optic disc signs of increased ICP in early childhood may occasionally be modified by the distensibility of the young skull. In the absence of conditions associated with early closure of sutures and early obliteration of the fontanel (craniostenosis, Crouzon disease, and Apert syndrome), infants with increased ICP may not develop papilledema. The differential diagnosis of papilledema includes structural changes of the disc (pseudopapilledema, pseudoneuritis, drusen, and myelinated nerve fibers), with which it may be confused, and the disc swelling of papillitis associated with optic neuritis in addition to the disc changes of hypertension and diabetes mellitus. Unless retinal hemorrhage or edema involves the macular area, the preservation of good central vision and the absence of an afferent pupillary defect (Marcus Gunn pupil) help to differentiate acute papilledema from the edema of the optic nerve head found in acute optic neuritis.

Papilledema is a neurologic emergency. It can be accompanied by other signs of increased ICP, including headaches, nausea, and vomiting. Neuroimaging should be performed; if no intracranial masses are detected, a lumbar puncture and determination of CSF pressure should follow.

**OPTIC NEURITIS**

This is any inflammation or demyelinization of the optic nerve with attendant impairment of function. The process is usually acute, with rapidly progressive loss of vision. It may be unilateral or bilateral. Pain on movement of the globe or pain on palpation of the globe may precede or accompany the onset of visual symptoms. There is decreased visual activity, decreased color vision and contrast sensitivity, a relative afferent pupillary defect, and a normal macula and peripheral retina.

When the retrobulbar portion of the nerve is affected without ophthalmoscopically visible signs of inflammation at the disc, the term retrobulbar optic neuritis is applied. When there is ophthalmoscopically visible evidence of inflammation of the nerve head, the term papillitis or intraocular optic neuritis is used. When there is involvement of both the retina and the papilla, the term optic neuritis is used.

In childhood, optic neuritis may occur as an isolated condition or as a manifestation of a neurologic or systemic disease. Optic neuritis may be secondary to inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Behcet disease, autoimmune optic neuritis); infections (tuberculosis, syphilis, Lyme disease, menigitis, viral encephalitis, HIV, or postinfectious disease); and toxic or nutritional disorders (methanol, ethambutol, vitamin B₁₂ deficiency). It may
signify one of the many demyelinating diseases of childhood (see Chapter 600). Although a significant percentage of adults who experience an episode of optic neuritis eventually develop other symptoms associated with multiple sclerosis (MS), young children with optic neuritis are seemingly at less risk (risk of MS is 19% within 20 yr). High-risk features suggestive of MS include visual acuity better than no light perception, periocular pain, acutely normal-appearing optic nerve, no retinal abnormalities, and abnormal MRI suggesting a demyelinating disease. Bilateral optic neuritis in children may be associated with acute disseminated encephalomyelitis or neuromyelitis optica (NMO or Devic disease). NMO is characterized by rapid and severe bilateral visual loss accompanied by transverse myelitis and paraplegia. Brainstem and occasionally involvement of the cortex may be seen on MRI. NMO-specific immunoglobulin G (directed to the aquaporin 4 water channel) is the diagnostic test of choice for Devic syndrome. Optic neuritis may also be secondary to an exogenous toxin or drug, such as with lead poisoning or as a complication of long-term high-dose treatment with chloramphenicol or vincristine. Extensive pediatric neurologic and ophthalmic investigation, including MRI and lumbar puncture, is usually required. Idiopathic NMO is associated with antiaquaporin 4 antibodies, otherwise known as NMO antibodies.

In most cases of acute optic neuritis, some improvement in vision begins within 1-4 wk after onset, and vision may improve to normal or near normal within weeks or months. The course varies with cause. Although central vision may fully recover, it is common to find permanent defects in other areas of visual function (contrast sensitivity, color, brightness sense, and motion perception). Recurrences may occur especially, but not universally, in patients who go on to develop MS.

A treatment trial demonstrated that high-dose intravenous methylprednisolone may help to speed the visual recovery in young adults, and it may prevent the development of MS in those at risk. Orally administered corticosteroids should not be used because they are associated with a significant increase in the recurrence rate of optic neuritis. It is unknown to what degree the results of the aforementioned trial may be extrapolated to optic neuritis in childhood. Eccluzumab, an inhibitor of complement C5, has had some success in reducing relapses in patients with NMO.

LEBER OPTIC NEUROPATHY

This entity is characterized by sudden loss of central vision occurring in the 2nd and 3rd decades of life, and primarily affects young males. A characteristic peripapillary telangiectatic microangiopathy occurs not only in the presymptomatic phase of involved eyes but also in a high number of asymptomatic offspring in the female line. Disc hyperemia and edema mark the acute phase of visual loss. One eye is usually affected before the other. Visual field loss and impaired color vision are also present. In time, progressive optic atrophy and vision loss usually ensue. The tortuous angiopathy becomes less obvious. Although visual function after the initial loss generally remains stable, a significant and sometimes complete recovery may occur in as many as 30% of affected individuals. This recovery may take place years or decades after the initial episode of acute vision loss. The peripapillary angiopathy, the lack of short-term remission, and the degree of symmetry serve to distinguish most cases of Leber disease from the optic neuritis of MS.

Leber optic neuropathy is maternally inherited and is caused by defective cytoplasmic mitochondrial DNA. Multiple point mutations in the mitochondrial DNA that lead to the development of the disorder have been found. Because of the mitochondrial nature of the disorder, skeletal and cardiac muscle disorders, including electrocardiographic abnormalities, may also be encountered in affected individuals.

OPTIC ATROPHY

This term denotes degeneration of optic nerve axons, with attendant loss of function. The ophthalmoscopic signs of optic atrophy are pallor of the disc and loss of substance of the nerve head, sometimes with enlargement of the disc cup. The associated vision defect varies with the nature and site of the primary disease or lesion.

Optic atrophy is the common expression of a wide variety of congenital or acquired pathologic processes. The cause may be traumatic, inflammatory, degenerative, neoplastic, or vascular; intracranial tumors and hydrocephalus are principal causes of optic atrophy in children. In some cases, progressive optic atrophy is hereditary. Dominantly inherited infantile optic atrophy is a relatively mild heredodegenerative type that tends to progress through childhood and adolescence. Autosomal recessively inherited congenital optic atrophy is a rare condition that is evident at birth or develops at a very early age; the visual defect is usually profound. Behr optic atrophy is a hereditary type associated with hypertonia of the extremities, increased deep tendon reflexes, mild cerebellar ataxia, some degree of mental deficiency, and possibly external ophthalmoplegia. This disorder affects principally boys age 3-11 yr. Some forms of heredodegenerative optic atrophy are associated with sensorineural hearing loss, as may occur in some children with juvenile-onset (insulin-dependent) diabetes mellitus. In the absence of an obvious cause, optic atrophy in an infant or child warrants extensive etiologic investigation.

OPTIC NERVE GLIOMA

Optic nerve glioma, more properly referred to as juvenile pilocytic astrocytoma, is the most frequent tumor of the optic nerve in childhood. This neuroglial tumor may develop in the intraorbital, intracanalicular, or intracranial portion of the nerve; the chiasm is often involved.

The tumor is a cytologic benign hamartoma that is generally stationary or only slowly progressive. The principal clinical manifestations when the tumor occurs in the intraorbital portion of the nerve are unilateral loss of vision, proptosis, and deviation of the eye; optic atrophy or congestion of the optic nerve head may occur. Chiasmal involvement may be attended by defects of vision and visual fields (often bitemporal hemianopia), increased ICP, papilledema or optic atrophy, hypothalamic dysfunction, pituitary dysfunction, and sometimes nystagmus or strabismus. Juvenile pilocytic astrocytomas occur with increased frequency in patients with neurofibromatosis.

Treatment of optic pathway gliomas is controversial. The best management is usually periodic observation with serial radiography (preferably MRI). Only symptomatic and radiographically progressing optic nerve gliomas require strong consideration for treatment. Surgical removal may be appropriate when the tumor is confined to the intraorbital, intracanalicular, or prechiasmal portion of the nerve if a patient has unsightly proptosis with complete or nearly complete loss of vision of the affected eye. When the chiasm is involved, resection is not usually indicated and radiation and chemotherapy may be necessary.

TRAUMATIC OPTIC NEUROPATHIES

Injury to the optic nerve may result from both direct and indirect trauma. Direct trauma to the optic nerve is a result of a penetrating injury to the orbit with transection or contusion of the nerve. Blunt trauma to the orbit may also lead to severe visual loss if the traumatic force is transmitted to the optic canal and causes disruption of the blood supply to the intracanalicular portion of the nerve. Treatment with high-dose corticosteroids has not been proven to be effective, and similar regimens have shown there is an increased relative risk of death when such regimens are given to patients after significant head injury.

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Chapter 632
Childhood Glaucoma
Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

Glaucoma is a general term used to indicate damage to the optic nerve with visual field loss that is caused by or related to elevated pressure within the eye. It is classified according to the age of the affected individual at presentation and the association of other ocular or systemic conditions. Glaucoma that begins within the 1st 3 yr of life is called infantile (congenital); that which begins between the ages of 3 and 30 yr is called juvenile.

Primary glaucoma indicates that the cause is an isolated anomaly of the drainage apparatus of the eye (trabecular meshwork). More than 50% of infantile cases are primary glaucoma. In secondary glaucoma, other ocular or systemic abnormalities are associated, even if a similar developmental defect of the trabecular meshwork is also present. Primary infantile glaucoma occurs with an incidence of 0.03% (Table 632-1).

**CLINICAL MANIFESTATIONS**
The symptoms of infantile glaucoma include the classic triad of epiphora (tearing), photophobia (sensitivity to light), and blepharospasm (eyelid squeezing; Fig. 632-1). Each can be attributed to corneal irritation. Only approximately 30% of affected infants demonstrate the classic symptom complex. Signs of glaucoma include corneal edema, corneal and ocular enlargement, and conjunctival injection (Fig. 632-2).

### Table 632-1 Primary and Secondary Childhood Glaucomas

<table>
<thead>
<tr>
<th>I. PRIMARY GLAUCOMAS</th>
<th>II. SECONDARY GLAUCOMAS</th>
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<td>A. Congenital open-angle glaucoma</td>
<td>A. Traumatic glaucoma</td>
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<td>1. Acute glaucoma</td>
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<td>2. Infantile</td>
<td>a. Angle concusion</td>
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<td>3. Late recognized</td>
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<td>B. Autosomal dominant juvenile glaucoma</td>
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<td>C. Primary angle-closure glaucoma</td>
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<td>D. Associated with systemic abnormalities</td>
<td>3. Arteriovenous fistula</td>
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<td>1. Sturge-Weber syndrome</td>
<td>a. Synechial angle closure</td>
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<tr>
<td>2. Neurofibromatosis type 1 (NF-1)</td>
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<td>3. Stickler syndrome</td>
<td>D. Lens-induced glaucoma</td>
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</tr>
<tr>
<td>1. Congenital glaucoma with iris and pupillary abnormalities</td>
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<td>2. Aniridia</td>
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<td>3. Congenital ocular melanosis</td>
<td>8. Posterior polymorphous dystrophy</td>
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<td>9. Idiopathic or familial elevated episcleral venous pressure</td>
</tr>
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<tr>
<td>7. Iridotrabecular dysgenesis and ectropion uveae</td>
<td>12. Congenital hereditary endothelial dystrophy</td>
</tr>
<tr>
<td>8. Posterior polymorphous dystrophy</td>
<td>13. Congenital hereditary iris stromal hypoplasia</td>
</tr>
</tbody>
</table>

Some infants and children with early-onset glaucoma have more extensive maldevelopment of the anterior segment of the eye. The neurocrystopathies comprise a spectrum of conditions relating to abnormal embryologic development of the anterior segment. They are usually bilateral and may include abnormalities of the iris, cornea, and lens. Other ocular anomalies that may be associated with glaucoma in infants and children are aniridia, cataract, spherophakia, and ectopia lentis. Glaucoma may also develop secondary to persistent hyperplastic primary vitreous or retinopathy of prematurity.

Trauma, intraocular hemorrhage, ocular inflammatory disease, and intraocular tumor are also important causes of glaucoma in the pediatric population. Systemic disorders associated with glaucoma in infants and children are Sturge-Weber syndrome (see Chapter 596.3), neurofibromatosis (see Chapter 596.1), Lowe syndrome, Marfan syndrome (see Chapter 702), congenital rubella (see Chapters 109.6 and 247), and a number of chromosomal syndromes (see Chapter 81).

Glaucoma occurs frequently in children with a history of congenital cataracts. Glaucoma may develop in up to 25% of children who have undergone cataract surgery early in life. The cause of aphakic glaucoma is not known but is thought to be the result of a coexistent anterior chamber deformity. Children treated for cataracts need to be monitored closely for this complication that may threaten vision.

**DIAGNOSIS AND TREATMENT**

The diagnosis of infantile glaucoma is made on recognition of the signs and symptoms. Once the diagnosis is established, treatment is started promptly. Unlike adult glaucoma, in which medication is often the first line of therapy, for infantile glaucoma, the treatment is primarily surgical. Procedures used to treat glaucoma in children include surgery to establish a more normal anterior chamber angle (goniotomy and trabeculotomy), to create a site for aqueous fluid to exit the eye (trabeculectomy and seton surgery), or to reduce aqueous fluid production (cyclocryotherapy and cyclophotocoagulation). Many children frequently require several operations to lower and maintain their IOP adequately, and long-term medical therapy may be necessary as well. Patients with multiple ocular abnormalities and those with aphakic glaucoma generally require more surgeries to achieve and maintain adequate IOP control. Although vision may be reduced secondary to glaucomatous optic nerve damage or corneal scarring, amblyopia is the most common cause of loss of vision in these children.

**Bibliography is available at Expert Consult.**

The sclera and cornea are more elastic in early childhood than later in life. An increase in intraocular pressure (IOP), therefore, leads to an expansion of the globe, including the cornea, and the development of buphthalmos (“ox eye”). If the cornea continues to enlarge, breaks occur in the endothelial basement membrane (Descemet membrane) and may lead to permanent corneal scarring. These breaks in Descemet membrane (Haab striae) are visible as horizontal edematous lines that cross or curve around the central cornea. They rarely occur beyond 3 yr of age or in corneas <12 mm in diameter. The cornea also becomes edematous and cloudy, with increased IOP. The corneal edema leads to tearing and photophobia. Glaucoma should be considered in a child suspected of having a nasolacrimal duct obstruction if any of these other signs or symptoms are present.

Children with unilateral glaucoma generally present early because the difference in the corneal size between the eyes can be noticed. When the disease is bilateral, parents may not recognize the increased corneal size. Many parents view the large eyes as attractive and do not seek help until other symptoms develop.

Cupping of the optic nerve head is detected by ocular examination. The optic nerve of an infant is easily distended by excessive pressure. Deep, central cupping readily occurs and may regress with normalization of pressure.
Bibliography
HYPERTELORISM AND HYPOTELORISM

Hypertelorism is wide separation of the eyes or an increased interorbital distance, which may occur as a morphogenetic variant, a primary deformity, or a secondary phenomenon in association with developmental abnormalities, such as frontal meningocele or encephalocele or the persistence of a facial cleft. Often associated are strabismus, generally exotropia, and sometimes optic atrophy.

Hypotelorism refers to narrowness of the interorbital distance, which may occur as a morphogenetic variant alone or in association with other anomalies, such as epicanthus or holoprosencephaly, or secondary to a cranial dystrophy, such as scaphocephaly.
EXOPHTHALMOS AND ENOPHTHALMOS
Protrusion of the eye is referred to as exophthalmos or proptosis and is a common indicator of orbital disease. It may be caused by shallowness of the orbits, as in many craniofacial malformations, or by increased tissue mass within the orbit, as with neoplastic, vascular, and inflammatory disorders. Ocular complications include exposure keratopathy, ocular motor disturbances, and optic atrophy with loss of vision.

Posterior displacement or sinking of the eye back into the orbit is referred to as enophthalmos. This may occur with orbital fracture or with atrophy of orbital tissue.

ORBITAL INFLAMMATION
Inflammatory disease involving the orbit may be primary or secondary to systemic disease. Idiopathic orbital inflammation (orbital pseudotumor) represents a wide spectrum of clinical entities. Symptoms at the time of presentation may include pain, eyelid swelling, proptosis, a red eye, and fever. The inflammation may involve a single extraocular muscle (myositis) or the entire orbit. Orbital apex syndrome is a serious condition that may also involve the cavernous sinus and may compress or displace the optic nerve. Confusion with orbital cellulitis is common but can be differentiated by the lack of associated sinus disease, its appearance on CT scan, and lack of improvement with systemic antibiotics. Orbital pseudotumor is associated with systemic lupus erythematosus, Crohn disease, myasthenia gravis, and lymphoma. Treatment includes the use of high-dose systemic corticosteroids. Often, the symptoms improve dramatically shortly after treatment is initiated. Bilateral involvement, associated uveitis, disc edema, and recurrence of inflammation are not uncommon in the pediatric population. Immunotherapy or radiation treatment may be necessary for resistant or recurrent cases.

Thyroid-related opthalmopathy (see also Chapter 563) is believed to be secondary to an immune mechanism, leading to inflammation and deposition of mucopolysaccharides and collagen in the extraocular muscles and orbital fat. Involvement of the extraocular muscles may lead to a restrictive strabismus. Lid retraction and exophthalmos may cause corneal exposure and infection or perforation. Involvement of the posterior orbit may compress the optic nerve. Treatment of thyroid-related opthalmopathy may include the use of systemic corticosteroids, radiation of the orbit, eyelid surgery, strabismus surgery, or orbital decompression to eliminate symptoms and protect vision. The degree of orbital involvement is often independent of the status of the systemic disease.

Other systemic disorders that may cause inflammatory disease within the orbit include lymphoma (see Chapter 496), sarcoidosis (see Chapter 165), amyloidosis (see Chapter 164), polyanteritis nodosa (see Chapter 167.3), systemic lupus erythematosus (see Chapter 158), dermatomyositis (see Chapter 159), Wegener granulomatosis (see Chapter 167), and juvenile xanthogranuloma (see Chapter 507).

TUMORS OF THE ORBIT
Various tumors occur in and about the orbit in childhood. Among benign tumors, the most common are vascular lesions (chiefly hemangiomas) (Fig. 633-1) and dermoids. Among malignant neoplasms, rhabdomyosarcoma, lymphosarcoma, and metastatic neuroblastoma are the most frequent. Optic nerve gliomas (see Chapter 631) are most commonly seen in patients with neurofibromatosis and may present with poor vision or proptosis. Retinoblastoma (see Chapter 502) may extend into the orbit if it is discovered late or goes untreated. Teratomas are rare tumors that typically grow rapidly after birth and exhibit explosive proptosis.

The effects of orbital tumors vary with their locations and growth patterns. The principal signs are proptosis, resistance to retroplacement of the eye, and impairment of eye movement. A palpable mass may be found. Other significant signs are ptosis, optic nerve head congestion, optic atrophy, and loss of vision. Bruit and visible pulsation of the globe are important clues to vascular lesions.

Evaluation of orbital tumors includes ultrasonography, MRI, and CT. Pseudotumor of the orbit also must be considered in children with signs of a mass lesion. In selected cases, an incisional or excisional biopsy of the lesion may be warranted.

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


Orbital infections are common in children. It is important to be able to distinguish the different forms of infection that occur in the orbital region to allow rapid diagnosis and treatment to prevent loss of vision or spread of the infection to the nearby intracranial structures (Table 634-1).

DACRYOADENITIS
Dacryoadenitis, or inflammation of the lacrimal gland, is uncommon in childhood. It may occur with mumps (in which case it is usually acute and bilateral, subsiding in a few days or weeks) or with infectious mononucleosis. *Staphylococcus aureus* may produce a suppurative dacryoadenitis. Chronic dacryoadenitis is associated with certain systemic diseases, particularly sarcoidosis, tuberculosis, and syphilis. Some systemic diseases may produce enlargement of the lacrimal and salivary glands (Mikulicz syndrome).

DACRYOCYSTITIS
Dacryocystitis is an infection of the lacrimal sac. Dacryocystitis generally requires obstruction of the nasolacrimal system to allow its development. Acute dacryocystitis presents with redness and swelling over the region of the lacrimal sac (Fig. 634-1). It is treated with warm compresses and systemic antibiotics. This helps to control the
infection, but the obstruction usually requires definitive treatment to reduce the risk of recurrence.

Dacryocystitis may occur in newborns as a complication of a congenital dacryocystocele (see Chapter 625). If present, systemic antibiotics and digital pressure for decompression are recommended. The obstruction of the nasolacrimal system may resolve once the infection clears. If spontaneous resolution does not occur, probing should be considered within a short time frame. An intranasal cyst may be present in conjunction with the dacryocystocele. If this occurs, marsupialization of the cyst may be needed at the time of the probing.

**PRESEPTAL CELLULITIS**

Inflammation of the lids and periorbital tissues without signs of true orbital involvement (such as proptosis or limitation of eye movement) is generally referred to as periorbital or preseptal cellulitis and is a form of facial cellulitis. This is common in young children and may be caused by bacteremia, sinusitis, trauma, an infected wound, or an abscess of the lid or periorbital region (pyoderma, hordeolum, conjunctivitis, dacryocystitis, insect bite). Patients present with eyelid swelling; the edema may be so intense as to make it difficult to evaluate the globe. Prior to the Haemophilus influenzae type B vaccine, the most common cause of pediatric preseptal (facial) cellulitis was bacteremia caused by H. influenzae type B. Group A streptococcus, S. aureus, and pneumococcus are common etiologic agents. Clinical examination will show lack of proptosis, normal ocular movement, and normal pupil function. CT examination will demonstrate edema of the lids and subcutaneous tissues anterior to the orbital septum (Fig. 634-2). Antibiotic therapy and careful monitoring for signs of sepsis and local progression are essential.

**ORBITAL CELLULITIS**

This is a condition involving inflammation of the tissues of the orbit, with proptosis, limitation of movement of the eye, edema of the conjunctiva (chemosis), and inflammation and swelling of the eyelids with potentially decreased visual acuity (see Table 634-1). The mean age is approximately 7 yr but the range is 10 mo–18 yr. Patients often feel ill with general symptoms of toxicity, fever, and leukocytosis (also see Chapter 194).

Orbital cellulitis may follow direct infection of the orbit from a wound, metastatic deposition of organisms during bacteremia, or more often direct extension or venous spread of infection from contiguous sites such as the lids, conjunctiva, globe, lacrimal gland, or nasolacrimal sac or, more commonly, from the paranasal (ethmoid) sinuses. In some cases, primary or metastatic tumor in the orbit can produce the clinical picture of orbital cellulitis. The most common cause of orbital cellulitis in children is paranasal sinusitis. The spread of infection to the orbit from the sinuses is more prevalent in children because of their thinner bony septa and sinus wall, greater porosity of bones, open suture lines, and larger vascular foramina. The spread of infection is also facilitated by the venous and lymphatic communicaton between the sinuses and surrounding structures, which allow flow in either direction, facilitating retrograde thrombophlebitis. Frequent pathogenic organisms include S. aureus, including methicillin-resistant S. aureus, streptococcus species (Streptococcus anginosus), and Haemophilus species.

The potential for complications is great. Visual loss can occur secondary to an increase in orbital pressure that causes retinal artery occlusion or optic neuritis. This is more likely to occur in the presence of an orbital abscess. Extension of infection from the orbit into the cranial cavity may lead to cavernous sinus thrombosis or meningitis, epidural or subdural empyema, or brain abscesses. Additional complications include optic atrophy, exposure keratitis, and retinal or choroidal ischemia. The differential diagnosis includes idiopathic orbital

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**Table 634-1** Chandler Classification of Orbital Complications of Sinusitis, a Clinical Description

<table>
<thead>
<tr>
<th>CHANDLER CLASS</th>
<th>STAGE</th>
<th>CLINICAL DESCRIPTION AND DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Inflammatory edema</td>
<td>Eyelid edema and erythema, normal extraocular movement, normal visual acuity</td>
</tr>
<tr>
<td>II</td>
<td>Orbital cellulitis</td>
<td>Diffuse edema of orbital contents without discrete abscess formation</td>
</tr>
<tr>
<td>III</td>
<td>Subperiosteal abscess</td>
<td>Collection of purulent exudate beneath periosteum of lamina papyracea, displacement of globe downward/laterally</td>
</tr>
<tr>
<td>IV</td>
<td>Orbital abscess</td>
<td>Purulent collection within orbit, proptosis, chemosis, ophthalmoplegia, decreased vision</td>
</tr>
<tr>
<td>V</td>
<td>Cavernous sinus thrombosis</td>
<td>Bilateral eye findings, proptosis, meningismus</td>
</tr>
</tbody>
</table>

*The radiographic correlation of a subperiosteal or orbital abscess is seen with CT is a contrast-enhancing mass in the extraconal or intraconal space, possibly with areas of cavitation, because purulence cannot be determined with CT scanning. From Rudloe TF, Harper M, Prabhu SP, et al: Acute periorbital infections: who needs emergent imaging? Pediatrics 125:e719–e726, 2010.*
inflammation, myositis, sarcoidosis, granulomatous vasculitis, leukemia, lymphoma, histiocytic disorders, rhabdomyosarcoma, ruptured dermoid cyst, orbital trauma, and orbital foreign body.

Orbital cellulitis must be recognized promptly and treated aggressively. Hospitalization and systemic antibiotic therapy are usually indicated. All patients require CT imaging of the orbit, including the surrounding central nervous system, preferably with intravenous contrast to detect a subperiosteal abscess, orbital abscess, or intracranial extension. Parenteral antibiotics must be started immediately. Antimicrobial agents should begin with vancomycin and cefotaxime (or ceftriaxone); some include metronidazole. If there is no evidence of improvement or if there are signs of progression, sinus drainage may be required. The presence of an orbital or subperiosteal abscess (Figs. 634-3 and 634-4) may require urgent drainage of the orbit. The clinical presentation and course of each individual patient should dictate the need and timing of abscess drainage.

Children <9 yr of age with a medial subperiosteal abscess can initially be managed with a trial of intravenous antibiotics, which usually is sufficient for resolution of the abscess. They must be examined frequently (every 6 hr until improvement) for signs of visual deterioration or pupillary abnormalities. Most will become afebrile within 48 hr and have exam improvement by 72 hr. If there are pupillary abnormalities, decreased vision, or failure to improve, the subperiosteal abscess should be drained. Many recommend routine drainage for a subperiosteal abscess in children >9 yr of age. If there is an orbital abscess with an abnormal physical exam, the recommendation is that drainage be performed and antibiotics given at the time of diagnosis. The use of adjunctive corticosteroids and anticoagulation for cavernous venous thrombosis and or superior ophthalmic vein thrombosis is controversial.

*bibliography is available at Expert Consult.*
Bibliography


Approximately 30% of all blindness in children results from trauma. Children and adolescents account for a disproportionate number of episodes of ocular trauma. Boys ages 11-15 yr are the most vulnerable; their injuries outnumber those in girls by a ratio of about 4:1. The majority of injuries are related to sports, sticks, stones, fireworks, paint balls, air-powered BB guns, and other projectiles. High-velocity projectiles and fireworks cause particularly devastating ocular and orbital injuries. Much of the trauma is avoidable (see Chapter 5.1). Any part of the orbit or globe may be affected (Fig. 635-1).

**ECCHYMOSIS AND SWELLING OF THE EYELIDS**

Ecchymosis and edema of the eyelids are common after blunt trauma (Fig. 635-2). These disorders are self-limiting, absorb spontaneously, and can be treated with iced compresses and analgesics. Periorbital ecchymosis should prompt careful examination of the eye and surrounding structures for more serious injuries such as orbital bone fracture, intraocular hemorrhage, or rupture of the globe.
Injuries to the Eye

**Chapter 635**  

**LACERATIONS OF THE EYELIDS**

Eyelid lacerations may vary from simple to complex. When evaluating an eyelid laceration, key findings include depth of the laceration, its location, and whether there is involvement of the canaliculus. Most superficial eyelid lacerations may be closed by the primary caregiver, but if a laceration is deep, involves the lid margin, or involves the canaliculus, it should be evaluated by an ophthalmologist. The levator muscle is responsible for elevation of the upper eyelid and runs deep to the skin and orbicularis oculi muscle. If the levator muscle is compromised and not recognized at initial repair, ptosis will occur. Therefore, if orbital fat is visible in the laceration, the laceration has compromised the skin, orbicularis oculi and levator muscles, and orbital septum and must be meticulously repaired to avoid ptosis. Eyelid margin involvement (Fig. 635-3) also requires careful repair to avoid lid malposition and notch formation. These can lead to ocular surface problems in the future, resulting in corneal scarring and loss of vision. Lacerations involving the canaliculus require intubation of the nasolacrimal system in addition to repair of the laceration of the eyelid to avoid future tearing problems. Proper primary repair of eyelid lacerations often achieves a superior outcome to secondary repair at a later date. As with any eyelid injury, careful examination of the eye and surrounding tissue is required.

**SUPERFICIAL ABRASIONS OF THE CORNEA**

When the corneal epithelium is scratched, abraded, or denuded, it exposes the underlying epithelial basement layer and superficial corneal nerves. This is accompanied by pain, tearing, photophobia, and decreased vision. Corneal abrasions are detected by instilling fluorescein dye and inspecting the cornea using a blue-filtered light (Fig. 635-4). A slit lamp is ideal for this examination, but a direct ophthalmoscope with blue filter or a handheld Wood lamp is adequate for young children.

**Treatment** of a corneal abrasion is directed at promoting healing and relieving pain. Abrasions are treated with frequent applications of a topical antibiotic ointment until the epithelium is completely healed. The use of a semipressure patch does not improve healing time or decrease pain. An improperly applied patch may itself abrade the cornea. A topical cycloplegic agent (cyclopentolate hydrochloride 1%) can relieve the pain from ciliary spasm in patients with large abrasions. Topical anesthetics should not be given at home because they retard epithelial healing and inhibit the natural blinking reflex.

**FOREIGN BODY INVOLVING THE OCULAR SURFACE**

This usually produces acute discomfort, tearing, and inflammation. Most foreign bodies can be detected by examination in good light with the aid of magnification (Fig. 635-5) or a direct ophthalmoscope set on a high plus lens (+10 or +12). In many cases, slit-lamp examination is necessary, especially if the particle is deep or metallic. Some
conjunctival foreign bodies tend to lodge under the upper eyelid, causing the sensation of corneal foreign body as they come into contact with the globe on eyelid movement; they may also produce vertically oriented linear corneal abrasions (Fig. 635-6). Finding these abrasions should lead to a suspicion of such a foreign body, and eversion of the lid may be necessary (see Chapter 619). If a foreign body is suspected but not found, further examination is indicated. If the history suggests injury with a high-velocity particle, radiologic examination of the eye may be needed to explore the possibility of an intraocular foreign body. Removal of a foreign body can be facilitated by instillation of a drop of topical anesthetic. Many foreign bodies can be removed by irrigation or by gently wiping them away with a moistened cotton-tipped applicator. Embedded foreign bodies or foreign bodies in the central cornea should be treated by an ophthalmologist. Removal of corneal foreign bodies may leave epithelial defects, which are treated as corneal abrasions. Metallic foreign bodies may cause rust to form in the corneal tissues; examination by an ophthalmologist 1 or 2 days after removal of a foreign body is recommended because a rust ring might require further treatment.

HYPHEMA
This is the presence of blood in the anterior chamber of the eye. It may occur with either a blunt or perforating injury and represents a situation that may threaten vision. Hyphema appears as a bright or dark red fluid level between the cornea and iris or as a diffuse murkiness of the aqueous humor. Children with hyphema present with acute loss of vision, with or without pain. The treatment of hyphema involves efforts to minimize the vision-threatening sequelae such as rebleeding, glaucoma, and corneal blood staining. Bedrest is necessary, with elevation of the head of the bed to 30 degrees. A shield (without underlying patch) is placed on the affected eye, and a cycloplegic agent is used to immobilize the iris. Additionally, topical or systemic steroids are used to minimize intraocular inflammation. Antiemetics should be considered if the patient is experiencing nausea. All nonsteroidal anti-inflammatory agents and aspirin must be avoided. Rarely, hospitalization and sedation may be necessary to ensure compliance in some children. If the intraocular pressure is elevated, topical and systemic pressure-lowering medications are used. If the pressure is not controllable by such measures, then surgical evacuation of the clot may be required to minimize the risk of permanent vision loss. Patients with sickle cell disease or trait are at higher risk of acute loss of vision secondary to elevated intraocular pressure or optic nerve infarction and may require more aggressive intervention. Individuals with a history of traumatic hyphema have an increased incidence of glaucoma later in life and should be monitored on a regular basis throughout their lives.

OPEN GLOBE
A penetrating, perforating, or blunt injury resulting in compromise of the cornea or sclera of the eye is one of the most sight-threatening injuries that can be sustained (Fig. 635-7). This is known as an open globe. An open globe is a true ophthalmologic emergency that requires prompt, careful evaluation and immediate repair to minimize vision loss. Perforation vision loss can result from corneal scarring, loss of intraocular contents, or infection. Evaluation involves careful history including time and mechanism of the injury, as well as visual acuity and inspection of the eye. A full-thickness corneal wound will often present with prolapsed iris tissue through the wound. If this is not immediately evident, a peaked or irregular pupil may be a sign of full-thickness laceration. Scleral compromise may be more difficult to identify because of overlying structures. The thinnest part of the sclera is at the corneoscleral junction (the limbus) and just posterior to the insertion of the rectus muscles. When an open globe is caused by blunt force injury, these are the 2 areas most likely involved. The overlying conjunctiva may not be compromised but a subconjunctival hemorrhage may be present, obscuring the view. In these cases, look for a shallow anterior chamber, low intraocular pressure, or pigment within the involved area. If the patient has been diagnosed with an open globe, the examination should be stopped, an eye shield placed immediately, and the ophthalmologist contacted to minimize further ocular compromise.

OPTIC NERVE TRAUMA
The optic nerve may be injured in both penetrating and blunt trauma. The injury may occur at any point between the globe and the chiasm. Traumatic injury to the optic nerve, regardless of cause or location, results in reduced vision and a pupillary defect. Direct trauma to the intraorbital optic nerve may cause transection, partial transection, or optic sheath hemorrhage. Fractures involving the skull base may cause injury to the intracranial portions of the optic nerve. Treatment decisions are difficult because there are no universally accepted guidelines, and the prognosis for good visual outcome is often poor. Medical management involves observation and the use of high-dose corticosteroids, although the use of corticosteroids has not been proven to improve visual outcomes and has been shown to increase the risk of death in patients with significant head injury. Surgical intervention
involves optic nerve sheath decompression for nerve sheath hemorrhages. If compression of the optic nerve is secondary to orbital hemorrhage, prompt lateral canthotomy and cantholysis should be performed to relieve intraorbital pressure. Decompression of the optic canal may be performed if there is compression of the optic nerve by a bone fragment. Optic canal decompression is controversial in the absence of direct bone compression.

**CHEMICAL INJURIES**

Chemical burns of the cornea and adnexal tissue are among the most urgent of ocular emergencies. Alkali burns are usually more destructive than acid burns because they react with fats to form soaps, which damage cell membranes, allowing further penetration of the alkali into the eye. Acids generally cause less severe, more localized tissue damage. The corneal epithelium offers moderate protection against weak acids, and little damage occurs unless the pH is 2.5 or less. Most stronger acids precipitate tissue proteins, creating a physical barrier against their further penetration.

Mild acid or alkali burns are characterized by conjunctival injection and swelling and mild corneal epithelial erosions. The corneal stroma may be mildly edematous, and the anterior chamber may have mild to moderate cell and flare reactions. With strong acids, the cornea and conjunctiva rapidly become white and opaque. The corneal epithelium may slough, leaving a relatively clear stroma; this appearance may initially mask the severity of the burn. Severe alkali burns are characterized by corneal opacification.

**Emergency treatment** of a chemical burn begins with immediate, copious irrigation with water or saline. Local debridement and removal of foreign particles should be performed as irrigation continues. If the nature of the chemical injury is unknown, the use of pH test paper is helpful in determining whether the agent was basic or acidic. Irrigation should continue for at least 30 min or until 2 L of irrigant has been instilled in mild cases and for 2-4 hr or until 10 L of irrigant has been instilled in severe cases. At the end of irrigation, the pH should be within a normal range (7.3-7.7). The pH should be checked again approximately 30 min after irrigation to ensure that it has not changed. The goal of treatment is to minimize sequelae that may threaten vision, such as conjunctival scarring, corneal scarring/opacification, glaucoma, cataract, and ptosis.

**ORBITAL FRACTURES**

The orbit is the bony structure surrounding the eye. Any of these bones may fracture in a traumatic incident. Superior and lateral wall fractures are the least common of the fracture sites, but superior orbital fracture is the most significant because of the potential of intracranial injury. The medial wall of the orbit is very susceptible to fracture because of the thin nature of the lamina papyracea. Perhaps the most common site of fracture from blunt trauma is the orbital floor. This is often referred to as blowout fracture. At times, the fracture may act as a trapdoor, entrapping orbital contents within the fracture site.

The patient often presents with a recent history of periorbital trauma and pain. Diplopia, eyelid swelling, eye movement restriction, or hypesthesia may or may not be present. Eye symptoms may be associated with nausea and bradycardia if the inferior rectus is entrapped in the fracture site. A complete ophthalmic examination, including, visual acuity, examination of the pupil for ocular alignment, ocular motility, anterior segment and fundus status, as well as the history of the injury, is required because there are often accompanying ocular injuries. The diagnosis of fracture is suspected if eye misalignment, eye movement restriction, or enophthalmos (sunken eye) is present. The diagnosis is verified by orbital CT scan.

Medical management includes iced compresses to the orbit and elevation for the head of the bed for the 1st 24-48 hr. Broad-spectrum antibiotics are sometimes recommended for 14 days because of the exposure of the orbital contents to the sinus cavity. In medial wall fractures, instructions not to blow one’s nose should be given to the patient to avoid orbital emphysema and subsequent optic nerve compression. Consider neurosurgical consultation in orbital roof fractures. Indications for surgical repair of orbital fractures are diplopia in

**primary gaze or downgaze that persists for 2 wk, enophthalmos, or fracture of the orbital floor involving more than half of the floor.** Extraocular muscle entrapment often requires prompt surgical repair because affected patients have significant pain, nausea, and vomiting that are difficult to control. Rarely, extraocular muscle entrapment can cause activation of the oculocardiac reflex, requiring urgent fracture repair.

**PENETRATING WOUNDS OF THE ORBIT**

These demand careful evaluation for possible damage to the eye, optic nerve, orbital contents, or brain. Examination should include investigation for a retained foreign body. Orbital hemorrhage and infection are common with penetrating wounds of the orbit; such injuries must be treated as emergencies.

**CHILD ABUSE**

See Chapter 40.

This is a major cause of injuries to the eye and orbital region. The possibility of nonaccidental trauma must be considered in any child with ecchymosis or laceration of the lids, hemorrhage in or about the eye, cataract or dislocated lens, retinal detachment, or fracture of the orbit. Inflicted childhood neurotrauma (shaken baby syndrome) occurs secondary to violent, nonaccidental, repetitive, unrestrained acceleration-deceleration head and neck movements, with or without blunt head trauma in children typically younger than 3 yr of age. Inflicted childhood neurotrauma accounts for approximately 10% of all cases of child abuse and carries a mortality rate of up to 25%. Detection of abuse is not only important in order to treat the pathology that is discovered but also to prevent further abuse or even death. The ocular manifestations are numerous and may have a prominent role in recognition of this syndrome. Retinal hemorrhage is the most common ophthalmic finding and occurs at all levels of the retina. The pattern of hemorrhage helps to distinguish this disorder from other causes of retinal hemorrhage or from accidental injuries (Fig. 635-8). Retinal hemorrhages can occur without associated intracranial pathology.

**FIREWORKS-RELATED INJURIES**

Injuries related to the use of fireworks can be the most devastating of all ocular traumas that occur in children. At least 20% of emergency department visits for fireworks-related injuries are for ocular trauma. In the United States, a majority of these injuries take place around Independence Day, and most occur despite adult supervision.

**SPORTS-RELATED OCULAR INJURIES AND THEIR PREVENTION**

Although sports injuries occur in all age groups, far more children and adolescents participate in high-risk sports than do adults. The
greater number of participating children, their athletic immaturity, and the increased likelihood of their using inadequate or improper eye protection account for their disproportionate share of sports-related eye injuries (see Chapters 688 and 693).

The sports with the highest risk of eye injury are those in which no eye protection can be worn, including boxing, wrestling, and martial arts. Other high-risk sports include those that use a rapidly moving ball or puck, bat, stick, racquet, or arrow (baseball, hockey, lacrosse, racquet sports, and archery) or involve aggressive body contact (football and basketball). Related to both risk and frequency of participation, the highest percentage of eye injuries are in basketball and baseball.

Protective eyewear, designed for a specific activity, is available for most sports. For basketball, racquet sports, and other recreational activities that do not require a helmet or face mask, molded polycarbonate sports goggles that are secured to the head by an elastic strap are suggested. For hockey, football, lacrosse, and baseball (batter), specific helmets with polycarbonate face shields and guards are available. Children should also wear sports goggles under the helmets. For baseball, goggles and helmets should be worn for batting, catching, and base running; goggles alone are usually sufficient for other positions.

**HANDHELD LASER RETINAL INJURY**

Handheld laser pointers, often purchased to light cigarettes or for other purposes, may produce significant retinal damage if the power output is ≥150 mW. If a person looks directly at the light, direct foveal injury may occur before he or she has time to blink. Central (foveal) blurring and decreased visual activity are the chief complaints. Retinal injuries include retinal disruption, subretinal edema, and macular holes (Fig. 635-9), which usually require surgical repair.

*Figure 635-9 Laser damage to the left eye. A, Color photo of the fundus of the left eye showing a macular hole. Note the changes at the retinal pigment epithelium. B, Infrared photo of the left fundus. C, Optical coherence tomography (OCT) of the left eye showing the macular hole. (From Petrou P, Patwary S, Banerjee PJ, et al: Bilateral macular hole from a handheld laser pointer, Lancet 383:1780, 2014.)*
Bibliography


Ch 636  General Considerations and Evaluation  Joseph Haddad Jr. and Sarah Keesecker

CLINICAL MANIFESTATIONS
Diseases of the ear and temporal bone typically manifest with 1 or more of 8 clinical signs and symptoms.

Otalgia usually is associated with inflammation of the external or middle ear, but it can represent pain referred from involvement of the teeth, temporomandibular joint, or pharynx. In young infants, pulling or rubbing the ear along with general irritability or poor sleep, especially when associated with fever, may be the only signs of ear pain. Ear pulling alone is not diagnostic of ear pathology.

Purulent otorrhea is a sign of otitis externa, otitis media with perforation of the tympanic membrane (TM), drainage from the middle ear through a patent tympanostomy tube, or, rarely, drainage from a first branchial cleft sinus. Bloody drainage may be associated with acute or chronic inflammation (often with granulation tissue and/or an ear tube), trauma, neoplasm, foreign body, or blood dyscrasia. Clear drainage suggests a perforation of the TM with a serious middle-ear effusion or, rarely, a cerebrospinal fluid leak draining through defects (congenital or traumatic) in the external auditory canal or from the middle ear.

Hearing loss results either from disease of the external or middle ear (conductive hearing loss) or from pathology in the inner ear, retrocochlear structures, or central auditory pathways (sensorineural hearing loss). The most common cause of hearing loss in children is otitis media (OM).

Swelling around the ear most commonly is a result of inflammation (e.g., external otitis, perichondritis, mastoiditis), trauma (e.g., hematoma), benign cystic masses, or neoplasm.

Vertigo is a specific type of dizziness that is defined as any illusion or sensation of motion. Dizziness is less specific than vertigo and refers to a sensation of altered orientation in space. Vertigo is an uncommon complaint in children; the child or parent might not volunteer information about balance unless asked specifically. The most common cause of dizziness in young children is eustachian tube–middle-ear disease, but true vertigo also may be caused by labyrinthitis, perilymphatic fistula between the inner and middle ear as a result of trauma or a congenital inner ear defect, cholesteatoma in the mastoid or middle ear, vestibular neuronitis, benign paroxysmal vertigo, Ménière disease, or disease of the central nervous system. Older children might describe a feeling of the room spinning or turning; younger children might express the dysequilibrium only by falling, stumbling, or clumsiness.

Nystagmus may be unidirectional, horizontal, or jerk nystagmus. It is vestibular in origin and usually is associated with vertigo.

Tinnitus rarely is described spontaneously by children, but it is common, especially in patients with eustachian tube–middle-ear disease or sensorineural hearing loss (SNHL). Children can describe tinnitus if asked directly about it, including laterality and the quality of the sound.

FACIAL PARALYSIS
The facial nerve may be dehiscent in its course through the middle ear in as many as 50% of patients. Infection with local inflammation, most commonly in acute OM, can lead to a temporary paralysis of the facial nerve. It also can result from Lyme disease, cholesteatoma, Bell palsy, Ramsay Hunt syndrome (herpes zoster oticus), fracture, neoplasm, or infection of the temporal bone. Congenital facial paralysis can result from birth trauma or congenital abnormality of the 7th nerve or from a syndrome such as Möbius or CHARGE (coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, and ear anomalies), or it may be associated with other cranial nerve abnormalities and craniofacial anomalies.

PHYSICAL EXAMINATION
Complete examination with special attention to the head and neck can reveal a condition that can predispose to or be associated with ear disease in children. The facial appearance and the character of speech can give clues to an abnormality of the ear or hearing. Many craniofacial anomalies, such as cleft palate, mandibulofacial dysostosis (Treacher Collins syndrome), and trisomy 21 (Down syndrome), are associated with disorders of the ear and eustachian tube. Mouth breathing and hypernasality can indicate intranasal or postnasal obstruction. Hypernasality is a sign of velopharyngeal insufficiency. Examining the oropharyngeal cavity might uncover an overt cleft palate or a submucous cleft (usually associated with a bifid uvula), both of which predispose to OM with effusion. A nasopharyngeal tumor with nasal and eustachian tube blockage may be associated with OM.

The position of the patient for examination of the ear, nose, and throat depends on the patient’s age and ability to cooperate, the clinical setting, and the examiner’s preference. The child can be examined on an examination table or in the parent’s lap. The presence of a parent or assistant usually is necessary to minimize movement and provide better examination results (Fig. 636-1). An examining table may be desirable for uncooperative older infants or when a procedure, such as microscopic evaluation or tympanocentesis, is performed. Wrapping the child in a sheet or using a papoose board can help to minimize movement. Lap examination is adequate and preferable in most infants and young children; the parent may assist in restraining the child by folding the child’s wrists and arms over the child’s own abdomen with one hand and holding the child’s head against the parent’s chest with the other hand. If necessary, the child’s legs can be held between the parent’s knees. To avoid ear trauma with movement, the examiner should hold the otoscope with the hand placed firmly against the child’s head or face, so that the otoscope moves with the head. Pulling up and out on the pinna straightens the ear canal and allows better exposure of the TM.

When examining the ear, inspecting the auricle and external auditory meatus for infection can aid in evaluating complications of OM. External otitis can result from acute OM with discharge, or inflammation of the posterior auricular area can indicate a periostitis or subperiosteal abscess extending from the mastoid air cells. The presence of preauricular pits or skin tags also should be noted because affected children have a slightly higher incidence of sensorineural hearing loss; ear pits can develop chronic infection.

Cerumen is a protective, waxy, water-repellent coating in the ear canal that can interfere with examination. Cerumen usually is removed using the surgical head of the otoscope, which allows passage of a wire loop or a blunt curette under direct visualization. Other methods include gentle irrigation of the ear canal with warm water, which should be performed only if the TM is intact, or instillation of a solution such as diluted hydrogen peroxide in the ear canal (with intact TM only) for a few minutes to soften the wax for suction removal or
irritation. Some commercial preparations such as trolamine polypeptide oleate-condensate (Cerumenex) can cause dermatitis of the external canal with chronic use and should be used only under a physician’s supervision.

Inflammation of the ear canal with associated pain often indicates external otitis. Abnormalities of the external auditory canal include stenosis (common in children with trisomy 21), bony exostoses, otitis, and the presence of foreign bodies. Cholesteatoma of the middle ear can manifest in the canal as intermittent foul-smelling drainage, sometimes associated with white debris; cholesteatoma of the external canal can appear as a white, pearl-like mass in the canal skin. White or gray debris of the canal suggests fungal external otitis. Newborn ear canals are filled with vernix caseosa, which is soft and pale yellow and should disappear shortly after birth.

The TM and its mobility are best assessed with a pneumatic otoscope. The normal TM is in a neutral position; a bulging TM may be caused by increased middle-air pressure, with or without pus or effusion in the middle ear; a bulging drum can obscure visualization of the malleus and annulus. Retraction of the TM usually indicates negative middle-air pressure, but it also can result from previous middle-air disease with fixation of the ossicles, ossicular ligaments, or TM. When retraction is present, the bony malleus appears more prominent, and the incus may be more visible posterior to the malleus.

The normal TM has a silvery-gray, “waxed paper” appearance (Fig. 636-2). A white or yellow TM can indicate a middle-air effusion. A red TM alone might not indicate pathology, because the blood vessels of the membrane may be engorged as a result of crying, sneezing, or nose blowing. A normal TM is translucent, allowing the observer to visualize the middle-air landmarks: incus, promontory, round window niche, and, often, the chorda tympani nerve. If a middle-air effusion is present, an air–fluid level or bubbles may be visible (Fig. 636-2). Inability to visualize the middle-air structures indicates opacification of the drum, usually caused by thickening of the TM or a middle-air effusion, or both. Assessment of the light reflex often is not helpful, because a middle ear with effusion reflects light as well as a normal ear.

TM mobility is helpful in assessing middle-air pressures and the presence or absence of fluid (see Fig. 636-2). To best perform pneumatic otoscopy, a speculum of adequate size is used to obtain a good seal and allow air movement in the canal. A rubber ring around the tip of the speculum can help to obtain a better canal seal. Normal middle-air pressure is characterized by a neutral TM position and brisk TM movement to both positive and negative pressures.

Eardrum retraction is most common when negative middle-air pressure is present; with even moderate negative middle-air pressure there is no visible inward movement with applied positive pressure in the ear canal (see Fig. 636-1). However, negative canal pressure, which is produced by releasing the rubber bulb of the pneumatic otoscope, can cause the TM to bounce out toward the neutral position. The TM can retract in both the presence and absence of middle-air fluid, and if the middle-air fluid is mixed with air, the TM might still have some mobility. Outward eardrum movement is less likely in the presence of severe negative middle-air pressure or middle-air effusion.

The TM that exhibits fullness (bulging) moves to applied positive pressure but not to applied negative pressure if the pressure within the middle ear is positive. A full TM and positive middle-air pressure without an effusion may be seen in young infants who are crying during the otoscopic examination, in older infants and children with nasal obstruction, and in the early stage of acute OM. When the middle-air–mastoid air cell system is filled with an effusion and little or no air is present, the mobility of the TM is severely decreased or absent in response to both applied positive and negative pressures.

![Figure 636-1 Methods of restraining an infant for examination and for procedures such as tympanocentesis or myringotomy. (From Bluestone CD, Klein JO: Otitis media in infants and children, ed 2, Philadelphia, 1995, WB Saunders, p. 91.)](image)

![Figure 636-2 A-F, Common conditions of the middle ear, as assessed with the otoscope. (From Bluestone CD, Klein JO: Otitis media in infants and children, ed 3, Philadelphia, 2001, WB Saunders, p. 131.)](image)
Tympanocentesis, or aspiration of the middle ear, is the definitive method of verifying the presence and type of a middle-ear effusion and is performed by inserting, through the inferior portion of the TM, an 18-gauge spinal needle attached to a syringe or a collection trap (Fig. 636-3). Culturing of the ear canal and alcohol cleansing should precede tympanocentesis and culture of the middle-ear aspirate; a canal culture is taken first to help determine whether organisms cultured from the middle ear are contaminants from the external canal or true middle-ear pathogens.

Further diagnostic studies of the ear and hearing include audiometric evaluation, impedance audiometry (tympanometry), acoustic reflectometry, and specialized eustachian tube function studies. Diagnostic imaging studies, including CT and MRI, often provide further information about anatomic abnormalities and the extent of inflammatory processes or neoplasms. Specialized assessment of labyrinthine function should be considered in the evaluation of a child with a suspected vestibular disorder (see Chapter 641).

Bibliography is available at Expert Consult.
Bibliography


The onset of hearing loss among children can occur at any time in childhood. When less-severe hearing loss or the transient hearing loss that commonly accompanies middle-ear disease in young children is considered, the number of affected children increases substantially.

**TYPES OF HEARING LOSS**

Hearing loss can be peripheral or central in origin. Peripheral hearing loss can be conductive, sensorineural, or mixed. **Conductive hearing loss** (CHL) commonly is caused by dysfunction in the transmission of sound through the external or middle ear or by abnormal transduction of sound energy into neural activity in the inner ear and the 8th nerve. CHL is the most common type of hearing loss in children and occurs when sound transmission is physically impeded in the external and/or middle ear. Common causes of CHL in the ear canal include atresia or stenosis, impacted cerumen, or foreign bodies. In the middle ear, perforation of the tympanic membrane (TM), discontinuity or fixation of the ossicular chain, otitis media (OM) with effusion, otosclerosis, and cholesteatoma can cause CHL.

Damage to or maldevelopment of structures in the inner ear can cause **sensorineural hearing loss** (SNHL). Causes include hair cell destruction from noise, disease, or ototoxic agents; cochlear malformation; perilymphatic fistula of the round or oval window membrane; and lesions of the acoustic division of the 8th nerve. A combination of CHL and SNHL is considered a mixed hearing loss.

An auditory deficit originating along the central auditory nervous system pathways from the proximal 8th nerve to the cerebral cortex usually is considered **central** (or retrocochlear) hearing loss. Tumors or demyelinating disease of the 8th nerve and cerebellopontine angle can cause hearing deficits but spare the outer, middle, and inner ear. These causes of hearing loss are rare in children. Other forms of central auditory deficits, known as central auditory processing disorders, include those that make it difficult even for children with normal hearing to listen selectively in the presence of noise, to combine information from the 2 ears properly, to process speech when it is slightly degraded, and to integrate auditory information when it is delivered faster although they can process it when delivered at a slow rate. These deficits can manifest as poor attention or as academic or behavior problems in school. Strategies for coping with such disorders are available for older children, and identification and documentation of the central auditory processing disorder often is valuable so that parents and teachers can make appropriate accommodations to enhance learning.

**ETIOLOGY**

Most CHL is acquired, with middle-ear fluid the most common cause. Congenital causes include anomalies of the pinna, external ear canal, TM, and ossicles. Rarely, congenital cholesteatoma or other masses in the middle ear manifest as CHL. TM perforation (e.g., trauma, OM), ossicular discontinuity (e.g., infection, cholesteatoma, trauma), tympanosclerosis, acquired cholesteatoma, or masses in the ear canal or middle ear (Langerhans cell histiocytosis, salivary gland tumors, glomus tumors, rhabdomyosarcoma) also can manifest as CHL. Uncommon diseases that affect the middle ear and temporal bone and can manifest with CHL include otosclerosis, osteopetrosis, fibrous dysplasia, and osteogenesis imperfecta.

SNHL may be congenital or acquired. Acquired SNHL may be caused by genetic, infectious, autoimmune, anatomic, traumatic, ototoxic, and idiopathic factors (Tables 637-1, 637-2, 637-3, and 637-4). The recognized risk factors account for approximately 50% of cases of moderate to profound SNHL.

**Sudden SNHL** in a previously healthy child is uncommon but may be from OM or other middle-ear pathologies such as autoimmune. Usually these causes are obvious from the history and physical examination. Sudden loss of hearing in the absence of obvious causes often is the result of a vascular event affecting the cochlear apparatus or nerve, such as embolism or thrombosis (secondary to prothrombotic conditions), or an autoimmune process. Additional causes include perilymph fistula, drugs, trauma, and the first episode of Ménière syndrome. In adults, sudden SNHL is often idiopathic and unilateral.

**INCIDENCE AND PREVALENCE**

Bilateral neural hearing loss is categorized as mild (20-30 dB), moderate (30-50 dB), severe (50-70 dB), or profound (>70 dB). The World Health Organization estimates that approximately 360 million people (5% of the world’s population, including 32 million children) have disabling hearing loss. An additional 364 million people have mild hearing loss. Half of these cases could have been prevented. In the United States, the average incidence of neonatal hearing loss is 1.1 in 1,000 infants; the rate by state varies from 0.22-3.61 in 1,000. Among United States, the average incidence of neonatal hearing loss is 1.1 in 1,000 infants; the rate by state varies from 0.22-3.61 in 1,000. Among persons from lower-income families.
Table 637-1  Indicators Associated with Hearing Loss

INDICATORS ASSOCIATED WITH SENSORINEURAL AND/OR CONDUCTIVE HEARING LOSS

**Neonates (Birth-28 Days) When Universal Screening Is Not Available**
- Family history of hereditary childhood sensorineural hearing loss
- In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
- Craniofacial anomalies, including those with morphologic abnormalities of the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
- Birthweight <1500 g (3.3 lb)
- Hyperbilirubinemia at a serum level requiring exchange transfusion
- Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics
- Bacterial meningitis
- Apger scores of 0-4 at 1 min or 0-6 at 5 min
- Mechanical ventilation lasting ≥5 days; extracorporeal membrane oxygenation
- Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; white forelock

**Infants and Toddlers (Age 29 Days-2 Yr) When Certain Health Conditions Develop That Require Rescreening**
- Parent or caregiver concern regarding hearing, speech, language, and/or developmental delay
- Bacterial meningitis and other infections associated with sensorineural hearing loss
- Head trauma associated with loss of consciousness or skull fracture
- Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; neurofibromatosis, osteopetrosis, and Usher Hunter, Waardenburg, Alport, Pendred, or Jervell and Lange-Nielsen syndrome
- Ototoxic medications, including but not limited to chemotherapeutic agents or aminoglycosides used in multiple courses or in combination with loop diuretics
- Recurrent or persistent otitis media with effusion for 3 mo or longer
- Skeletal dysplasia

**Infants and Toddlers (Age 29 Days-3 Yr) Who Require Periodic Monitoring of Hearing**
- Some newborns and infants pass initial hearing screening but require periodic monitoring of hearing to detect delayed-onset sensorineural and/or conductive hearing loss. Infants with these indicators require hearing evaluation at least every 6 mo until age 3 yr, and at appropriate intervals thereafter

**INDICATORS ASSOCIATED WITH DELAYED-ONSET SENSORINEURAL HEARING LOSS**
- Family history of hereditary childhood hearing loss
- In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
- Neurofibromatosis type 2 and neurodegenerative disorders
- Cogan syndrome (vasculitis: keratitis, uveitis, vertigo, dermatitis)

**INDICATORS ASSOCIATED WITH CONDUCTIVE HEARING LOSS**
- Recurrent or persistent otitis media with effusion
- Anatomic deformities and other disorders that affect eustachian tube function
- Neurodegenerative disorders

*Note: At all ages, parents’ concern about hearing loss must be taken seriously even in the absence of risk factors.*
*Adapted from American Academy of Pediatrics, Joint Committee on Infant Hearing: Joint Committee on Infant Hearing 1994 position statement, Pediatrics 95:152, 1995.*

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Table 637-2  Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>GENE</th>
<th>AUDIO PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFN3</td>
<td>POU3F4</td>
<td>Conductive hearing loss as a result of stapes fixation mimicking otosclerosis; superimposed progressive SNHL</td>
</tr>
<tr>
<td>DFN1</td>
<td>DIAPH1</td>
<td>Low-frequency loss beginning in the 1st decade and progressing to all frequencies to produce a flat audio profile with profound losses throughout the auditory range</td>
</tr>
<tr>
<td>DFN2</td>
<td>KCNO4</td>
<td>Symmetric high-frequency sensorineural loss beginning in the 1st decade and progressing over all frequencies</td>
</tr>
<tr>
<td></td>
<td>GJB3</td>
<td>Symmetric high-frequency sensorineural loss beginning in the 3rd decade</td>
</tr>
<tr>
<td>DFN3</td>
<td>GJB2</td>
<td>Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment</td>
</tr>
<tr>
<td></td>
<td>GJB6</td>
<td>Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment</td>
</tr>
<tr>
<td>DFN6, 14, and 38</td>
<td>WFS1</td>
<td>Early-onset low-frequency sensorineural hearing loss; approximately 75% of families dominantly segregating this audio profile carry missense mutations in the C-terminal domain of wolframin</td>
</tr>
<tr>
<td>DFN8, and 12</td>
<td>TECTA</td>
<td>Early-onset stable bilateral hearing loss, affecting mainly mid to high frequencies</td>
</tr>
<tr>
<td>DFN10</td>
<td>EYA4</td>
<td>Progressive loss beginning in the 2nd decade as a flat to gently sloping audio profile that becomes steeply sloping with age</td>
</tr>
<tr>
<td>DFN11</td>
<td>MYO7A</td>
<td>Ascending audiogram affecting low and middle frequencies at young ages and then affecting all frequencies with increasing age</td>
</tr>
<tr>
<td>DFN13</td>
<td>COL11A2</td>
<td>Congenital midfrequency sensorineural loss that shows age-related progression across the auditory range</td>
</tr>
<tr>
<td>DFN15</td>
<td>POU4F3</td>
<td>Bilateral progressive sensorineural loss beginning in the 2nd decade</td>
</tr>
</tbody>
</table>
### Table 637-2 Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss—cont’d

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>GENE</th>
<th>AUDIO PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFNA20, and 26</td>
<td>ACTG1</td>
<td>Bilateral progressive sensorineural loss beginning in the 2nd decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases</td>
</tr>
<tr>
<td>DFNA22</td>
<td>MYO6</td>
<td>Postlingual, slowly progressive, moderate to severe hearing loss</td>
</tr>
<tr>
<td>DFNB1</td>
<td>GJB2, GJB6</td>
<td>Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying 1 35delG allele and any other GJB2 SNHL-causing allele variant; in children carrying 2 GJB2 SNHL-causing missense mutations, severe to profound deafness is not observed</td>
</tr>
<tr>
<td>DFNB3</td>
<td>MYO7A</td>
<td>Severe to profound sensorineural hearing loss</td>
</tr>
<tr>
<td>DFNB4</td>
<td>SLC26A4</td>
<td>DFNB4 and Pendred syndrome (see Table 637-3) are allelic. DFNB4 hearing loss is associated with dilution of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss also is common</td>
</tr>
<tr>
<td>DFNB7, and 11</td>
<td>TMC1</td>
<td>Severe-to-profound prelingual hearing impairment</td>
</tr>
<tr>
<td>DFNB9</td>
<td>OTOF</td>
<td>OTOF-related deafness is characterized by 2 phenotypes: prelingual nonsyndromic hearing loss and, less frequently, temperature-sensitive nonsyndromic auditory neuropathy. The nonsyndromic hearing loss is bilateral severe-to-profound congenital deafness</td>
</tr>
<tr>
<td>DFNB12</td>
<td>CDH23</td>
<td>Depending on the type of mutation, recessive mutations of CDH23 can cause nonsyndromic deafness or type 1 Usher syndrome (USH1), which is characterized by deafness, vestibular areflexia, and vision loss as a result of retinitis pigmentosa</td>
</tr>
<tr>
<td>DFNB16</td>
<td>STRC</td>
<td>Early-onset nonsyndromic autosomal recessive sensorineural hearing loss</td>
</tr>
<tr>
<td>mtDNA 1555A &gt; G</td>
<td>12S rRNA</td>
<td>Degree of hearing loss varies from mild to profound but usually is symmetric; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy</td>
</tr>
</tbody>
</table>


### Table 637-3 Common Types of Syndromic Sensorineural Hearing Loss

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENE</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOMINANT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waardenburg (WS1)</td>
<td>PAX3</td>
<td>Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected 1st-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral</td>
</tr>
<tr>
<td>Waardenburg (WS2)</td>
<td>MITF, others</td>
<td>Major diagnostic criteria are as for WS1 but without dystopia canthorum. Approximately 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral</td>
</tr>
<tr>
<td>Branchiootorena</td>
<td>EYA1</td>
<td>Diagnostic criteria include hearing loss (98%), preauricular pits (85%), and branchial (70%), renal (40%), and external-ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed, and mild to profound in degree</td>
</tr>
<tr>
<td>CHARGE syndrome</td>
<td>CHD7</td>
<td>Choanal atresia, colobomas, heart defect, retardation, genital hypoplasia, ear anomalies, deafness. Can lead to sensorineural or mixed hearing loss. Can be autosomal dominant or isolated cases.</td>
</tr>
<tr>
<td>Goldenhar syndrome</td>
<td>Unknown</td>
<td>Part of the hemifacial microsomia spectrum. Facial hypoplasia, ear anomalies, hemivertebrae, parotid gland dysfunction. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic</td>
</tr>
</tbody>
</table>

| **RECESSIVE** |            |                                                                            |
| Pendred syndrome | SLC26A4 | Diagnostic criteria include sensorineural hearing loss that is congenital, nonprogressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilatation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goiter |
| Alport syndrome | COL4A3, COL4A4, and COL4A5 | Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected 1st-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral |
| Usher syndrome type 1 (USH1) | USH1A, MYO7A, USH1C, CDH23, USH1E, PCDH15, USH1G | Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nystagmus become severe enough to be noticeable) |
| Usher syndrome type 2 (USH2) | USH2A, USH2B, USH2C, others | Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic |
| Usher syndrome type 3 (USH3) | USH3 | Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function |

it may be associated with tinnitus and vertigo. Identifiable causes of
sudden SNHL include infections (Epstein-Barr virus, varicella-zoster
virus, herpes simplex virus), vascular injury to the cochlea, endolymphatic hydrops, and autoimmune inflammatory diseases. In most
patients with sudden SNHL, no etiology is discovered, and it is termed
idiopathic sudden SNHL.

**Infectious Causes**

The most common infectious cause of congenital SNHL is cytomegalo-
virus (CMV), which infects 1 in 100 newborns in the United States
(see Chapters 255 and 638). Of these, 6,000–8,000 infants each yr
have clinical manifestations, including approximately 75% with SNHL.
Congenital CMV warrants special attention because it is associated
with hearing loss in its symptomatic and asymptomatic forms, and the
hearing loss may be progressive. Some children with congenital CMV
have suddenly lost residual hearing at 4-5 yr of age. Much less common
congenital infectious causes of SNHL include toxoplasmosis and syph-
itis. Congenital CMV, toxoplasmosis, and syphilis also can manifest
with delayed onset of SNHL months to years after birth. Rubella, once
the most common viral cause of congenital SNHL, is very uncommon
because of effective vaccination programs. In utero infection with
herpes simplex virus is rare, and hearing loss is not an isolated
manifestation.

Other postnatal infectious causes of SNHL include neonatal group
B streptococcal sepsis and bacterial meningitis at any age. *Streptococcus
pneumoniae* is the most common cause of bacterial meningitis that
results in SNHL after the neonatal period and has become less common
with the routine administration of pneumococcal conjugate vaccine.
*Haemophilus influenzae* type b, once the most common cause of men-
ingitis resulting in SNHL, is rare owing to the *H. influenzae* type b
conjugate vaccine. Uncommon infectious causes of SNHL include
Lyme disease, parvovirus B19, and varicella. Mumps, rubella, and
rubeola, all once common causes of SNHL in children, are rare owing
to vaccination programs.

**Genetic Causes**

Genetic causes of SNHL probably are responsible for as many as 50%
of SNHL cases (see Tables 637-2 and 637-3). These disorders may be
associated with other abnormalities, may be part of a named syndrome,
or can exist in isolation. SNHL often occurs with abnormalities of the
ear and eye and with disorders of the metabolic, musculoskeletal,
integumentary, renal, and nervous systems.

**autosomal dominant** hearing losses account for approximately
10% of all cases of childhood SNHL. Waardenburg (types I and II) and
branchiootorenal syndromes represent 2 of the most common autosom-
al dominant syndrome types of SNHL. Types of SNHL are coded
with a 4 letter code and a number, as follows: DFN = deafness, A =
dominant, B = recessive, and number = order of discovery, for example,
DFNA 13. Autosomal dominant conditions in addition to those just
discussed include DFNA 1-18, 20-25, 30, 36, 38, and mutations in the
crystallin gene (*CRYM*).

**Autosomal recessive** genetic SNHL, both syndromic and nonsyn-
dromic, accounts for approximately 80% of all childhood cases of
SNHL. Usher syndrome (types 1, 2, and 3; all associated with blindness,
retinitis pigmentosa), Pendred syndrome, and the Jervell and Lange-
Nielsen syndrome (one form of the long Q-T syndrome) are 3 of the
most common syndromic recessive types of SNHL. Other autosomal
recessive conditions include Alström syndrome, type 4 Bartter syn-
drome, biotinidase deficiency, and DFNB 1-18, 20-23, 26-27, 29-33,
35-40, 42, 44, 46, 48, 49, 53, and 55.

Unlike children with an easily identified syndrome or with anomalies
of the outer ear, who may be identified as being at risk for hearing
loss and consequently monitored adequately, children with nonsyn-
dromic hearing loss present greater diagnostic difficulty. Mutations of
the connexin-26 and -30 genes have been identified in autosomal
recessive (DFNB 1) and autosomal dominant (DFNA 3) SNHL and in
sporadic patients with nonsyndromic SNHL; up to 50% of nonsyn-
dromic SNHLs may be related to a mutation of connexin-26. Mutations of the *GJB2* gene colocalize with DFNA 3 and DFNB 1 loci on
chromosome 13, are associated with autosomal nonsyndromic suscept-
tibility to deafness, and are associated with as many as 30% of cases of
sporadic severe to profound congenital deafness and 50% of cases of
autosomal recessive nonsyndromic deafness. In addition, mutations in
*GJB6* are associated with approximately 5% of recessive nonsyndromic
deafness. Sex-linked disorders associated with SNHL thought to
account for 1-2% of SNHLs include Norrie disease, the otopalatal
digital syndrome, Nance deafness, and Alport syndrome. Chromo-
somal abnormalities such as trisomy 13-15, trisomy 18, and trisomy
21 also can be accompanied by hearing impairment. Patients with
Turner syndrome have monosomy for all or part of 1 X chromosome
and can have CHL, SNHL, or mixed hearing loss. The hearing loss may be
progressive. Mitochondrial genetic abnormalities also can result in
SNHL (see Table 637-2).

Many genetically determined causes of hearing impairment, both
syndromic and nonsyndromic, do not express themselves until some-
time after birth. Alport, Alström, Down, and Hunter-Hurler syn-
dromes and von Recklinghausen disease are genetic diseases that
can have SNHL as a late manifestation.

**Physical Causes**

Agenesia or malformation of cochlear structures, including the Scheibe,
Mondini (Fig. 637-1), Alexander, and Michel anomalies, and semicircular canal anomalies, may be genetic. These anomalies
probably occur before the 8th wk of gestation and result from arrest in
normal development or aberrant development, or both. Many of these
anomalies also have been described in association with other congeni-
tal conditions such as intrauterine CMV and rubella infections. These
abnormalities are quite common; in as many as 20% of children with
SNHL, obvious or subtle temporal bone abnormalities are seen on
high-resolution CT scanning or MRI.

Conditions, diseases, or syndromes that include craniofacial abnor-
malities may be associated with CHL and possibly with SNHL. Pierre
Robin, Treacher Collins, Klippel-Feil, Crouzon, and branchiooto-
tenal syndromes and osteogenesis imperfecta often are associated with
hearing loss. Congenital anomalies causing CHL include malforma-
tions of the ossicles and middle-ear structures and atresia of the exter-
nal auditory canal.

SNHL also can occur secondary to exposure to toxins, chemicals,
and antimicrobials. Early in pregnancy, the embryo is particularly vul-
nerable to the effects of toxic substances. Ototoxic drugs, including
aminoglycosides, loop diuretics, and chemotherapeutic agents (cisplatin)
also can cause SNHL. Congenital SNHL can occur secondary to

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**Table 637-4** Infectious Pathogens Implicated in Sensorineural Hearing Loss in Children

<table>
<thead>
<tr>
<th>CONGENITAL INFECTIONS</th>
<th>ACQUIRED INFECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td><em>Borrelia burgdorferi</em></td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td><em>Epstein-Barr virus</em></td>
</tr>
<tr>
<td>Rubella virus</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td><em>Lassa virus</em></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Measles virus</td>
</tr>
</tbody>
</table>

It is important to note that infectious causes of SNHL are rare among children, and vaccination programs have significantly reduced the incidence of some causes, such as mumps, rubella, and meningitis. However, persistent infections can lead to hearing loss, and early identification and treatment are crucial. **Lancet** 365:879–890, 2005. From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet 365:879–890, 2005.
EFFECTS OF HEARING IMPAIRMENT

The effects of hearing impairment depend on the nature and degree of the hearing loss and on the individual characteristics of the child. Hearing loss may be unilateral or bilateral, conductive, sensorineural, or mixed; mild, moderate, severe, or profound; of sudden or gradual onset; stable, progressive, or fluctuating; and affecting a part or all of the audible spectrum. Other factors, such as intelligence, medical or physical condition (including accompanying syndromes), family support, age at onset, age at time of identification, and promptness of intervention, also affect the impact of hearing loss on a child.

Most hearing-impaired children have some usable hearing. Only 6% of those in the hearing-impaired population have bilateral profound hearing loss. Hearing loss very early in life can affect the development of speech and language, social and emotional development, behavior, attention, and academic achievement. Some cases of hearing impairment are misdiagnosed because affected children have sufficient hearing to respond to environmental sounds and can learn some speech and language but when challenged in the classroom cannot perform to full potential.

Even mild or unilateral hearing loss can have a detrimental effect on the development of a young child and on school performance. Children with such hearing impairments have greater difficulty when listening conditions are unfavorable (e.g., background noise and poor acoustics), as can occur in a classroom. The fact that schools are auditory-verbal environments is unappreciated by those who minimize the impact of hearing impairment on learning. Hearing loss should be considered in any child with speech and language difficulties or below-par performance, poor behavior, or inattention in school (Table 637-5).

Children with moderate, severe, or profound hearing impairment and those with other handicapping conditions often are educated in classes or schools for children with special needs. The auditory management and choices regarding modes of communication and education for children with hearing handicaps must be individualized, because these children are not a homogeneous group. A team approach to individual case management is essential, because each child and family unit has unique needs and abilities.

IDENTIFICATION OF HEARING IMPAIRMENT

The impact of hearing impairment is greatest on an infant who has yet to develop language; consequently, identification, diagnosis, description, and treatment should begin as soon as possible. In general, infants with a prenatal or perinatal history that puts them at risk (see Table 637-2) or those who have failed a formal hearing screening should be monitored closely by an experienced clinical audiologist until a reliable
assessments of auditory function have been obtained. Pediatricians should encourage families to cooperate with the follow-up plan. Infants who are born at risk but who were not screened as neonates (often because of transfer from one hospital to another) should have a hearing screening by age 3 mo.

Hearing-impaired infants, who are born at risk or are screened for hearing loss in a neonatal hearing screening program, account for only a portion of hearing-impaired children. Children who are congenitally deaf because of autosomal recessive inheritance or subclinical congenital infection often are not identified until 1-3 yr of age. Usually, those

### Table 637-5: Hearing Handicap as a Function of Average Hearing Threshold Level of the Better Ear

<table>
<thead>
<tr>
<th>AVERAGE THRESHOLD LEVEL (dB) AT 500-2,000 Hz (ANSI)</th>
<th>DESCRIPTION</th>
<th>COMMON CAUSES</th>
<th>WHAT CAN BE HEARD WITHOUT AMPLIFICATION</th>
<th>DEGREE OF HANDICAP (IF NOT TREATED IN 1ST YR OF LIFE)</th>
<th>PROBABLE NEEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15</td>
<td>Normal range</td>
<td>Conductive hearing loss</td>
<td>All speech sounds</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>16-25</td>
<td>Slight hearing loss</td>
<td>Otitis media, TM perforation, tympanosclerosis; eustachian tube dysfunction; some SNHL</td>
<td>Vowel sounds heard clearly, may miss unvoiced consonant sounds</td>
<td>Mild auditory dysfunction in language learning Difficulty in perceiving some speech sounds</td>
<td>Consideration of need for hearing aid, speech reading, auditory training, speech therapy, appropriate surgery, preferential seating</td>
</tr>
<tr>
<td>26-30</td>
<td>Mild</td>
<td>Otitis media, TM perforation, tympanosclerosis, severe eustachian dysfunction, SNHL</td>
<td>Hears only some speech sounds, the louder voiced sounds</td>
<td>Auditory learning dysfunction Mild language retardation Mild speech problems Inattention</td>
<td>Hearing aid Lip reading Auditory training Speech therapy Appropriate surgery</td>
</tr>
<tr>
<td>31-50</td>
<td>Moderate hearing loss</td>
<td>Chronic otitis, ear canal/middle ear anomaly, SNHL</td>
<td>Misses most speech sounds at normal conversational level</td>
<td>Speech problems Language retardation Learning dysfunction Inattention</td>
<td>All of the above, plus consideration of special classroom situation</td>
</tr>
<tr>
<td>51-70</td>
<td>Severe hearing loss</td>
<td>SNHL or mixed loss due to a combination of middle-ear disease and sensorineural involvement</td>
<td>Hears no speech sound of normal conversations</td>
<td>Severe speech problems Language retardation Learning dysfunction Inattention</td>
<td>All of the above; probable assignment to special classes</td>
</tr>
<tr>
<td>71+</td>
<td>Profound hearing loss</td>
<td>SNHL or mixed</td>
<td>Hears no speech or other sounds</td>
<td>Severe speech problems Language retardation Learning dysfunction Inattention</td>
<td>All of the above; probable assignment to special classes or schools</td>
</tr>
</tbody>
</table>

ANSI, American National Standards Institute; SNHL, sensorineural hearing loss; TM, tympanic membrane.


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Figure 637-2: Hearing-assessment algorithm within an office visit. CMV, cytomegalovirus; ENT, ear, nose, and throat. (From Harlor AD Jr, Bower C. Clinical report—hearing assessment in infants and children: recommendations beyond neonatal screening, Pediatrics 124:1252–1263, 2009, Fig. 1, p. 1254.)
with more-severe hearing loss are identified at an earlier age, but identification often occurs later than the age at which intervention can provide an optimal outcome. Children who hear normally develop an extensive language by 3-4 yr of age (Table 637-6) and exhibit behavior reflecting normal auditory function (Table 637-7). Failure to fulfill these criteria should be the reason for an audiologic evaluation. Parents’ concern about hearing and any delayed development of speech and language should alert the pediatrician, because parents’ concern usually precedes formal identification and diagnosis of hearing impairment by 6 mo to 1 yr of age.

**CLINICAL AUDIOLOGIC EVALUATION**

Even the youngest infants can be evaluated for auditory function. When hearing impairment is suspected in a young child, reliable and valid estimates of auditory function can be obtained. Successful treatment strategies for hearing-impaired children rely on prompt identification and ongoing assessment to define the dimensions of auditory function. Cooperation among the pediatrician and specialists in areas such as audiology, speech and language pathology, education, and child development is necessary to optimize auditory-verbal development.

Therapy for hearing-impaired children includes considering and often fitting an amplification device, using a frequency modulation system in the classroom, monitoring hearing and auditory skills, counseling parents and families, advising teachers, and dealing with public agencies.

**Audiometry**

The technique of the audiologic evaluation varies as a function of the age or developmental level of the child, the reason for the evaluation, and the child’s otologic condition or history. An audiogram provides the fundamental description of hearing sensitivity (Fig. 637-3). Hearing thresholds are assessed as a function of frequency using pure tones (sine waves) at octave intervals from 250-8,000 Hz. Earphones typically are used when age-appropriate, and hearing is assessed independently for each ear. Air-conducted signals are presented through earphones (or loudspeakers) and are used to provide information about the sensitivity of the auditory system. These same test sounds can be delivered to the ear through an oscillator that is placed on the head, usually on the mastoid. Such signals are considered bone-conducted because the bones of the skull transmit vibrations as sound energy directly to the inner ear, essentially bypassing the outer and middle ears. In a normal ear, and also in children with SNHL, the air- and bone-conduction thresholds are the same. In those with CHL, the air- and bone-conduction thresholds differ. This is called the air–bone gap, which indicates the amount of hearing loss attributable to dysfunction in the outer and/or middle ear. With mixed hearing loss, both the bone- and air-conduction thresholds are abnormal, and there is an air–bone gap.

**Speech-Recognition Threshold**

Another measure useful for describing auditory function is the speech-recognition threshold (SRT), which is the lowest intensity level at which a score of approximately 50% correct is obtained on a task of recognizing spondees. Spondees words are 2 syllable words or phrases that have equal stress on each syllable, such as baseball, hotdog.

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Table 637-6  Criteria for Referral for Audiologic Assessment

<table>
<thead>
<tr>
<th>AGE (mo)</th>
<th>REFERRAL GUIDELINES FOR CHILDREN WITH “SPEECH” DELAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>No differentiated babbling or vocal imitation</td>
</tr>
<tr>
<td>18</td>
<td>No use of single words</td>
</tr>
<tr>
<td>24</td>
<td>Single-word vocabulary of ≤10 words</td>
</tr>
<tr>
<td>30</td>
<td>&lt;100 words; no evidence of 2 word combinations; unintelligible</td>
</tr>
<tr>
<td>36</td>
<td>&lt;200 words; no use of telegraphic sentences; clarity &lt;50%</td>
</tr>
<tr>
<td>48</td>
<td>&lt;600 words; no use of simple sentences; clarity ≤80%</td>
</tr>
</tbody>
</table>


Table 637-7  Guidelines for Referral of Children with Suspected Hearing Loss

<table>
<thead>
<tr>
<th>AGE (mo)</th>
<th>NORMAL DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>Should startle to loud sounds, quiet to mother’s voice, momentarily cease activity when sound is presented at a conversational level</td>
</tr>
<tr>
<td>5-6</td>
<td>Should correctly localize to sound presented in a horizontal plane, begin to imitate sounds in own speech repertoire or at least reciprocally vocalize with an adult</td>
</tr>
<tr>
<td>7-12</td>
<td>Should correctly localize to sound presented in any plane; respond to name, even when spoken quietly</td>
</tr>
<tr>
<td>13-15</td>
<td>Should point toward an unexpected sound or to familiar objects or persons when asked</td>
</tr>
<tr>
<td>16-18</td>
<td>Should follow simple directions without gestural or other visual cues; can be trained to reach toward an interesting toy at midline when a sound is presented</td>
</tr>
<tr>
<td>19-24</td>
<td>Should point to body parts when asked; by 21-24 mo, can be trained to perform play audiometry</td>
</tr>
</tbody>
</table>


Figure 637-3 Audiogram showing bilateral conductive hearing loss.
and pancake. Listeners must be familiar with all the words for a valid test result to be obtained. The SRT should correspond to the average of pure-tone thresholds at 500, 1,000, and 2,000 Hz, the pure-tone average. The SRT is relevant as an indicator of a child’s potential for development and use of speech and language; it also serves as a check of the validity of a test because children with nonorganic hearing loss (malingerers) might show a discrepancy between the pure-tone average and SRT.

The basic battery of hearing tests concludes with an assessment of a child’s ability to understand monosyllabic words when presented at a comfortable listening level. Performance on such word intelligibility tests assists in the differential diagnosis of hearing impairment and provides a measure of how well a child performs when speech is presented at loudness levels similar to those encountered in the environment.

**Play Audiometry**

Hearing testing is age dependent. For children at or above the developmental level of a 5–6 yr old, conventional test methods can be used. For children 30 mo to 5 yr of age, play audiometry can be used. Responses in play audiometry usually are conditioned motor activities associated with a game, such as dropping blocks in a bucket, placing rings on a peg, or completing a puzzle. The technique can be used to obtain a reliable audiogram for a preschool child. For those who will not or cannot repeat words clearly for the SRT and word intelligibility tests, pictures can be used with a pointing response.

**Visual Reinforcement Audiometry**

For children between the ages of about 6 mo and 30 mo, visual reinforcement audiometry (VRA) commonly is used. In this technique, the child is observed for a head-turning response on activation of an animated (mechanical) toy reinforcer. If infants are properly conditioned, by giving sounds associated with the visual toy cue, VRA can provide reliable estimates of hearing sensitivity for tones and speech sounds. In most applications of VRA, sounds are presented by loudspeakers in a sound field, so no ear-specific information is obtained.

Assessment of an infant often is designed to rule out hearing loss that would affect the development of speech and language. Normal sound-field response levels of infants indicate sufficient hearing for this purpose despite the possibility of different hearing levels in the 2 ears.

**Behavioral Observation Audiometry**

Used as a screening device for infants <3 mo of age, behavioral observation audiometry is limited to unconditioned, reflexive responses to complex (not frequency-specific) test sounds such as noise, speech, or music presented using calibrated signals from a loudspeaker or uncalibrated noisemakers. Response levels can vary widely within and among infants and usually do not provide a reliable estimate of sensitivity. Assessment of a child with suspected hearing loss is not complete until pure-tone hearing thresholds and SRTs (a reliable audiogram) have been obtained in each ear. Behavioral observation audiometry and VRA in sound-field testing give estimates of hearing responsivity in the better-hearing ear.

**Acoustic Immittance Testing**

Acoustic immittance testing is a standard part of the clinical audiologic test battery and includes tympanometry. It is a useful objective assessment technique that provides information about the status of the middle ear. Tympanometry can be performed in a physician’s office and is helpful in the diagnosis and management of OM with effusion, a common cause of mild to moderate hearing loss in young children.

**Tympanometry**

Tympanometry provides a graph of the middle ear’s ability to transmit sound energy (admittance, or compliance) or impede sound energy (impedance) as a function of air pressure in the external ear canal. Because most immittance test instruments measure acoustic admittance, the term **admittance** is used here. The principles apply to whatever units of measurement are used.

A probe is inserted into the entrance of the external ear canal so that an airtight seal is obtained. The probe varies air pressure, presents a tone, and measures sound pressure level in the ear canal through the probe assembly. The sound pressure measured in the ear canal relative to the known intensity of the probe signal is used to estimate the acoustic admittance of the ear canal and middle-ear system. Admittance can be expressed in a unit called a millimho (mmho) or as a volume of air (mL) with equivalent acoustic admittance. The test is performed so that an estimate can be made of the volume of air enclosed between the probe tip and TM. The acoustic admittance of this volume of air is deducted from the overall admittance measure to obtain a measure of the admittance of the middle-ear system alone. Estimating ear canal volume also has a diagnostic benefit, because an abnormally large value is consistent with the presence of an opening in the TM (perforation or tube).

Once the admittance of the air mass in the external auditory canal has been eliminated, it is assumed that the remaining admittance measure accurately reflects the admittance of the entire middle-ear system. Its value is controlled largely by the dynamics of the TM. Abnormalities of the TM can dictate the shape of tympanograms, thus obscuring abnormalities medial to the TM. In addition, the frequency of the probe tone, the speed and direction of the air pressure change, and the air pressure at which the tympanogram is initiated can all influence the outcome.

When air pressure in the ear canal is equal to that in the middle ear, the middle-ear system is functioning optimally. Therefore, the ear canal pressure at which there is the greatest flow of energy (admittance) should be a reasonable estimate of the air pressure in the middle-ear space. This pressure is determined by finding the maximum or **peak admittance** on the tympanogram and obtaining its value on the x-axis. The value on the y-axis at the tympanogram peak is an estimate of peak admittance based on admittance tympanometry (Table 637-8). This peak measure sometimes is referred to as **static acoustic admittance**, even though it is estimated from a dynamic measure.

**Tympanometry in Otitis Media with Effusion**

Children who have OM with effusion often have reduced peak admittance or high negative tympanometric peak pressures (see Fig. 640-SC in Chapter 640). However, in the diagnosis of effusion, the tympanometric measure with the greatest sensitivity and specificity is the shape of the tympanogram rather than its peak pressure or admittance. This shape sometimes is referred to as the tympanometric gradient or width; it measures the degree of roundness or **peakedness** of the tympanogram. The more rounded the peak (or, in an absent peak, a flat

---

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>ADMITTANCE (mL)</th>
<th>Speed of Air Pressure Sweep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤50 daPa/sec*</td>
</tr>
<tr>
<td>Children</td>
<td>Lower limit</td>
<td>0.30</td>
</tr>
<tr>
<td>(3–5 yr)</td>
<td>Median</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Upper limit</td>
<td>0.90</td>
</tr>
<tr>
<td>Adults</td>
<td>Lower limit</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Upper limit</td>
<td>1.36</td>
</tr>
</tbody>
</table>

*Ear canal volume measurement based on admittance at lowest tail of tympanogram.
†Ear canal measurement based on admittance at lowest tail of tympanogram for children and at ≥200 daPa for adults.
dPa, decaPascals.
Tymanogram), the higher is the probability that an effusion is present (see Fig. 640–5B in Chapter 640). It is important to know which instrument is used, because some compute gradient automatically but others do not.

**Acoustic Reflex Test**

The acoustic reflex test also is part of the immittance test battery. With a properly functioning middle-ear system, admittance at the TM changes on activation of the stapedius and tensor tympani muscles. In healthy ears, the stapedial reflex occurs after exposure to loud sounds. Admittance instruments are designed to present reflex activating signals (pure tones of various frequencies or noise), either to the same ear or the contralateral ear, while monitoring admittance. Very small admittance changes that are time locked to presentations of the signal are considered to be a result of middle-ear muscle reflexes. Admittance changes may be absent when the hearing loss is sufficient to prevent the signal from reaching the loudness level necessary to elicit the reflex or when a middle-ear condition affects the ear’s ability to monitor a small admittance change. Reflexes usually are absent in patients with CHL because of the presence of an abnormal transfer system; thus, the acoustic reflex test is useful in the differential diagnosis of hearing impairment. The acoustic reflex test also is used in the assessment of SNHL and the integrity of the neurologic components of the reflex arc, including cranial nerves VII and VIII.

**Auditory Brainstem Response**

The auditory brainstem response (ABR) test is used to screen newborn hearing, confirm hearing loss in young children, obtain ear-specific information in young children, and test children who cannot, for whatever reason, cooperate with behavioral test methods. It also is important in the diagnosis of auditory dysfunction and of disorders of the auditory nervous system. The ABR test is a far-field recording of minute electrical discharges from numerous neurons. The stimulus, therefore, must be able to cause simultaneous discharge of the large numbers of neurons involved. Stimuli with very rapid onset, such as clicks or tone bursts, must be used. Unfortunately, the rapid onset required to create a measurable ABR also causes energy to be spread in the frequency domain, reducing the frequency-specificity of the response. The ABR result is not affected by sedation or general anesthesia. Infants and children from about 4 mo to 4 yr of age routinely are sedated to minimize electrical interference caused by muscle activity during testing. The ABR also can be performed in the operating room when a child is anesthetized for another procedure. Children younger than 4 mo of age might sleep for a long enough period of time after feeding to allow an ABR to be done.

The ABR can be recorded as 5–7 waves. Waves I, III, and V can be obtained consistently in all age groups; waves II and IV appear less consistently. The latency of each wave (time of occurrence of the wave peak after stimulus onset) increases, and the amplitude decreases with reductions in stimulus intensity or loudness; latency also decreases with increasing age, with the earliest waves reaching mature latency values earlier in life than the later waves. The ABR test has 2 major uses in a pediatric setting. As an audiometric test, it provides information on the ability of the peripheral auditory system to transmit information to the auditory nerve and beyond. It also is used in the differential diagnosis or monitoring of central nervous system pathology. For audiometry, the goal is to find the minimum stimulus intensity that yields an observable ABR. Plotting latency vs intensity for various waves also aids in the differential diagnosis of hearing impairment. A major advantage of auditory assessment using the ABR test is that ear-specific threshold estimates can be obtained on infants or patients who are difficult to test. ABR thresholds using click stimuli correlate best with behavioral hearing thresholds in the higher frequencies (1,000–4,000 Hz); responsivity in the low frequencies requires different stimuli (tone bursts or filtered clicks) or the use of masking, neither of which isolates the low-frequency region of the cochlea in all cases, and this can affect interpretation.

The ABR test does not assess “hearing.” It reflects auditory neuronal electrical responses that can be correlated to behavioral hearing thresholds, but a normal ABR result only suggests that the auditory system, up to the level of the midbrain, is responsive to the stimulus used. Conversely, a failure to elicit an ABR indicates an impairment of the system’s synchronous response but does not necessarily mean that there is no “hearing.” The behavioral response to sound sometimes is normal when no ABR can be elicited, such as in neurologic demyelinating disease. The ABR test may be used to infer whether and at what level of the auditory system impairment exists.

Hearing losses that are sudden, progressive, or unilateral are indications for ABR testing. Although it is believed that the different waves of the ABR reflect activity in increasingly rostral levels of the auditory system, the neural generators of the response have not been precisely determined. Each ABR wave beyond the earliest waves probably is the result of neural firing at many levels of the system, and each level of the system probably contributes to several ABR waves. High-intensity click stimuli are used for the neurologic application. The morphology of the response and wave and interwave latencies are examined in respect to age-appropriate forms. Delayed or missing waves in the ABR test often have diagnostic significance.

The ABR and other electrical responses are extremely complex and difficult to interpret. A number of factors, including instrumentation design and settings, environment, degree and configuration of hearing loss, and patients’ characteristics, can influence the quality of the recording. Therefore, testing and interpretation of electrophysiologic activity as it possibly relates to hearing should be carried out by trained audiologists to avoid the risk that unreliable or erroneous conclusions will affect a patient’s care.

**Otoacoustic Emissions**

During normal hearing, OAEs originate from the hair cells in the cochlea and are detected by sensitive amplifying processes. They travel from the cochlea through the middle ear to the external auditory canal, where they can be detected using miniature microphones. Transient evoked OAEs (TEOAEs) may be used to check the integrity of the cochlea. In the neonatal period, detection of OAEs can be accomplished during natural sleep, and TEOAEs can be used as screening tests in infants and children for hearing at the 30 dB level of hearing loss. They are less time consuming and elaborate than ABRs and are more sensitive than behavioral tests in young children. TEOAEs are reduced or absent owing to various dysfunctions in the middle and inner ears. They are absent in patients with >30 dB of hearing loss and are not used to determine the hearing threshold; rather, they provide a screen for whether hearing is present at >30–40 dB. Diseases such as OM or congenitally abnormal middle-ear structures reduce the transfer of TEOAEs and may incorrectly indicate a cochlear hearing disorder. If a hearing loss is suspected based on the absence of OAEs, the ears should be examined for evidence of pathology, and then ABR testing should be used for confirmation and identification of the type, degree, and laterality of hearing loss.

**Acoustic Reflectometry**

In acoustic reflectometry, a handheld instrument is placed next to the opening of a child’s ear canal and an 80 dB sound is delivered that varies in frequency from 2,000–4,500 Hz in a 100 msec period. The instrument measures the total level of reflected and transmitted sound. Some physicians have found this device useful to help gauge the presence or absence of middle-ear fluid, and a commercial version is marketed to parents as a way to monitor ear fluid. The instrument does not provide any information about hearing; if the presence of chronic fluid is suggested, audiometric evaluation should be obtained.

**TREATMENT**

With the use of universal hearing screening in the majority of states within the United States, the early diagnosis and treatment of children with hearing loss is common. Testing for hearing loss is possible even in very young children, and it should be done if parents suspect a
problem. Any child with a known risk factor for hearing loss should be evaluated in the 1st 6 mo of life.

Once a hearing loss is identified, a full developmental and speech and language evaluation is needed. Counseling and involvement of parents are required in all stages of the evaluation and treatment or rehabilitation. A CHL often can be corrected through treatment of a middle-ear effusion (i.e., ear tube placement) or surgical correction of the abnormal sound-conducting mechanism. Children with SNHL should be evaluated for possible hearing aid use by a pediatric audiologist. Hearing aids may be fitted for children as young as 2 mo of age. Compelling evidence from the hearing screening program in Colorado shows that identification and amplification before age 6 mo makes a very significant difference in the speech and language abilities of affected children, compared with cases identified and amplified after the age of 6 mo. In these children, repeat audiologic testing is needed to reliably identify the degree of hearing loss and to fine-tune the use of hearing aids.

Infants and young children with profound congenital or prelingual onset of deafness have benefited from multichannel cochlear implants (Fig. 637-4). These implants bypass injury to the organ of Corti and provide neural stimulation by way of an external microphone and a signal processor that digitizes auditory stimuli into digital radiofrequency impulses. Cochlear implantation before age 2 yr (and even 1 yr) improves hearing and speech, enabling more than 90% of children to be in mainstream education. Most develop age-appropriate auditory perception and oral language skills.

A serious complication of cochlear implants is an excessively high incidence of pneumococcal meningitis. All children receiving a cochlear implant must be vaccinated with the pneumococcal polyvalent vaccine PCV13 (Table 637-9).

Table 637-9 Recommended Pneumococcal Vaccination Schedule for Persons with Cochlear Implants

<table>
<thead>
<tr>
<th>AGE AT FIRST PCV13 DOSE (mo)*</th>
<th>PCV12 PRIMARY SERIES</th>
<th>PCV13 ADDITIONAL DOSE</th>
<th>PPV23 DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>3 doses, 2 mo apart†</td>
<td>1 dose at 12-15 mo of age†</td>
<td>Indicated at ≥24 mo of age†</td>
</tr>
<tr>
<td>7-11</td>
<td>2 doses, 2 mo apart†</td>
<td>1 dose at 12-15 mo of age†</td>
<td>Indicated at ≥24 mo of age†</td>
</tr>
<tr>
<td>12-23</td>
<td>2 doses, 2 mo apart†</td>
<td>Not indicated</td>
<td>Indicated at ≥24 mo of age†</td>
</tr>
<tr>
<td>24-59</td>
<td>2 doses, 2 mo apart†</td>
<td>Not indicated</td>
<td>Indicated†</td>
</tr>
<tr>
<td>≥60</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Indicated†</td>
</tr>
</tbody>
</table>

*A schedule with a reduced number of total 13-valent pneumococcal conjugate vaccine (PCV13) doses is indicated if children start late or are incompletely vaccinated. Children with a lapse in vaccination should be vaccinated according to the catch-up schedule (see Chapter 182).

†For children vaccinated at younger than age 1 yr, minimum interval between doses is 4 wk.

‡The additional dose should be administered 8 wk or more after the primary series has been completed.

§Children younger than age 5 yr should complete the PCV13 series first: 23-valent pneumococcal polysaccharide vaccine (PPV23) should be administered to children 24 mo of age or older 8 wk or more after the last dose of PCV13 (see Chapter 182). (Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP], MMWR Recomm Rep 49[RR-9]:1–35, 2000, and Licensure of a 13-valent pneumococcal conjugate vaccine [PCV13] and recommendations for use among children—Advisory Committee on Immunization Practices [ACIP], 2010, MMWR Morb Mortal Wkly Rep 59[9]:258–261, 2010.)

¶Minimum interval between doses is 8 wk.

§PCV13 is not recommended generally for children age 5 yr or older.

PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.


![Figure 637-4](image)

Figure 637-4 All cochlear implants share key components, including a microphone, speech processor, and transmitter coil, shown in a behind-the-ear position in this diagram. The microphone and speech processor pick up environmental sounds and digitize them into coded signals. The signals are sent to the transmitter coil and relayed through the skin to the internal device imbedded in the skull. The internal device converts the code to electronic signals, which are transmitted to the electrode array wrapping around the cochlea. The inset shows the radiographic appearance of the stimulating electrode array. (Reproduced with permission from MED-EL Corporation, Innsbruck, Austria. From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet 365:879–890, 2005.)

GENETIC COUNSELING

Families of children with the diagnosis of SNHL or a syndrome associated with SNHL and/or CHL should consider genetic counseling, which will allow a discussion of the likelihood of similar diagnoses in future pregnancies. The geneticist also can help in the evaluation and further testing of the patient with hearing loss to establish a diagnosis.

Bibliography is available at Expert Consult.
The external and middle ears, derived from the first and second branchial arches and grooves, grow throughout puberty, but the inner ear, which develops from the otocyst, reaches adult size and shape by midfetal development. The ossicles are derived from the first and second arches (malleus and incus), and the stapes arises from the second arch and the otic capsule. The malleus and incus achieve adult size and shape by the 15th wk of gestation, and the stapes achieves adult size and shape by the 18th wk of gestation. Although the pinna, ear canal, and tympanic membrane (TM) continue to grow after birth, congenital abnormalities of these structures develop during the first half of gestation. Malformed external and middle ears may be associated with serious renal anomalies, mandibulofacial dysostosis, hemifacial microsomia, and other craniofacial malformations. Facial nerve abnormalities may be associated with any of the congenital abnormalities of the ear and temporal bone. Malformations of the external and middle ears also may be associated with abnormalities of the inner ear and both conductive (CHL) and sensorineural hearing loss (SNHL).

Congenital ear problems may be minor and mainly cosmetic, or major, affecting both appearance and function. Any child born with an abnormality of the pinna, external auditory canal, or TM should have a complete audiologic evaluation in the neonatal period. Imaging studies are necessary for evaluation and treatment; in the patient with other craniofacial abnormalities a team approach with other specialists can assist in guiding therapy.

PINNA MALFORMATIONS
Severe malformations of the external ear are rare, but minor deformities are common. Isolated abnormalities of the external ear occur in approximately 1% of children. A pit-like depression just in front of the helix and above the tragus may represent a cyst or an epidermis-lined fistulous tract. These are common, with an incidence of approximately 8 in 1,000 children, and may be unilateral or bilateral and familial. The pits require surgical removal only if there is recurrent infection. Accessory skin tags, with an incidence of 1-2/1,000 live births, can be removed for cosmetic reasons by simple ligation if they are attached by a narrow pedicle. If the pedicle is broad-based or contains cartilage, they can be transplanted. Isolated anomalies of the shape and volume of the aerated portion of the pinna may indicate subtle abnormalities of the size, shape, and location of the pinna and ear canal, or major abnormalities with only small nubbins of skin and cartilage and the absence of the ear canal opening; anotia indicates complete absence of the pinna and ear canal. Microtia can be associated with serious renal anomalies, mandibulofacial dysostosis, hemifacial microsomia, and other craniofacial malformations. Facial nerve abnormalities may be associated with any of the congenital abnormalities of the ear and temporal bone. Malformations of the external and middle ears also may be associated with abnormalities of the inner ear and both conductive (CHL) and sensorineural hearing loss (SNHL).

Congenital ear problems may be minor and mainly cosmetic, or major, affecting both appearance and function. Any child born with an abnormality of the pinna, external auditory canal, or TM should have a complete audiologic evaluation in the neonatal period. Imaging studies are necessary for evaluation and treatment; in the patient with other craniofacial abnormalities a team approach with other specialists can assist in guiding therapy.

CONGENITAL STENOSIS OR ATRESIA OF THE EXTERNAL AUDITORY CANAL
Stenosis or atresia of the ear canal often occurs in association with congenital atresia of the auricle and middle ear. Malformations can occur in isolation or as part of a genetic syndrome. For example, the ear canal is narrow in trisomy 21 and external canal stenosis or atresia is common in branchiooculo facial syndrome, leading to CHL. Audiometric evaluation of these children should be undertaken as early in life as possible. Most children with significant CHL secondary to bilateral atresia wear bone conduction hearing aids for the 1st several yr of life. Diagnosis, evaluation, and surgical planning often are aided by CT, and sometimes MRI, of the temporal bone. Mild cases of ear canal stenosis do not require surgical enlargement unless the patient develops chronic external otitis or severe cerumen impaction that affects hearing.

Reconstructive ear canal and middle-ear surgery for atresia usually is considered for children older than 5 yr of age who have bilateral deformities resulting in a significant CHL. The aim of reconstructive surgery is to improve hearing to a point where the child may not need a hearing aid or to provide an ear canal and pinna so that the child can derive improved benefit from an air-conduction hearing aid. Hearing results for atresioplasty range from fair to excellent. CT evidence of an adequate middle-ear cleft, ossicles, and mastoid is required to perform the surgery; the position of the facial nerve, which often is in an abnormal location in these children, also must be considered (Fig. 638-1). The use of bone-anchored hearing aids is a safe, reliable, and low-risk alternative to atresioplasty and hearing results are generally excellent. Bone-anchored hearing aids may also be useful for rehabilitation of nonoptimal atresioplasty hearing results. These devices are approved by the U.S. Food and Drug Administration for surgical placement in children age 5 yr and older; prior to age 5 yr, they can be worn with a soft band around the head. Disadvantages include the fact that cosmesis is not very good (a bone-anchored hearing aid has a visible titanium abutment and snap-on hearing aid) and frequent wound care is required.

CONGENITAL MIDDLE-EAR MALFORMATIONS
Children may have congenital abnormalities of the middle ear as an isolated defect or in association with other abnormalities of the temporal bone, especially the ear canal and pinna, or as part of a syndrome. Affected children usually have CHL but may have mixed CHL and SNHL. Most malformations involve the ossicles, with the incus most commonly affected. Other less-common abnormalities of the middle ear include persistent stapedial artery, high-riding jugular bulb, and abnormalities of the shape and volume of the aerated portion of the middle ear and mastoid; all present problems for a surgeon. Depending on the type of abnormality and the presence of other anomalies, surgery may be considered to improve hearing.

CONGENITAL INNER EAR MALFORMATIONS
Congenital inner ear malformations have been identified and classified as a result of improvements in imaging modalities, especially CT and MRI. As many as 20% of children with SNHL may have anatomic abnormalities identified on CT or MRI. Congenital malformations of the inner ear usually are associated with SNHL of various degrees, from mild to profound. These malformations may occur as isolated anomalies or in association with other syndromes, genetic abnormalities, or structural abnormalities of the head and neck. Enlarged vestibular
The ear implants between the first and second branchial arch remnants, and residual amniotic fluid squamous debris. Congenital or acquired cholesteatoma should be suspected when deep retraction pockets, keratin debris, chronic drainage, aural granulation tissue, or a mass behind or involving the TM is present. Besides acting as a benign tumor causing local bone destruction, the keratinaceous debris of a cholesteatoma is a good culture medium and may become a focus of infection for chronic otitis media. Complications include ossicular erosion with hearing loss, bone erosion into the inner ear with dizziness, or exposure of the dura, with consequent meningitis or a brain abscess. Cholesteatoma should be removed surgically after CT scan (Fig. 638-2) and hearing evaluation, and appropriate antibiotic therapy. A second-look procedure 6-9 mo after primary surgery is often recommended to prevent further recurrence. Higher initial stage of disease, erosion of ossicles, cholesteatoma abutting or enveloping the incus or stapes, and need for removal of the ossicles are associated with increased likelihood of residual cholesteatoma. In addition, more extensive disease at initial surgery is associated with poorer hearing outcomes. Recurrence rates vary and are related to the extent of involvement at the time of surgery. In a large case series, recurrence rates were found to be as follows: 14% when disease was confined to 1 quadrant, 33% when more than 1 quadrant was involved but the ossicles and mastoids were not, 41% with ossicular involvement, and 67% with mastoid involvement. Overall recurrence may be as high as 57%. Congenital cholesteatoma is an aggressive disease, and early surgical

Figure 638-1 External auditory canal atresia on CT scans. A, Coronal scan of right ear shows absent external auditory canal with thick bony atresia plate (white arrows). Malleus neck is rotated and fused to superior portion of atresia plate (black arrow). B, Axial scan through attic shows fused ossicular mass (arrow). C, Coronal scan more posterior to A shows mastoid segment of facial nerve canal positioned more anteriorly than normal (arrows). D, Axial scan more inferior to B shows anterior-posterior mastoid segment of the facial nerve en face (arrow). Note abnormally close relationship to mandibular condyle. (From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 44-7, p. 584.)

audioducts have been identified on imaging studies in association with SNHL; although no therapy exists for this condition, it may be associated with progressive SNHL in some children, and, therefore, diagnosis may have some prognostic value.

Congenital perilymphatic fistula of the oval or round window membrane may present as a rapid-onset, fluctuating, or progressive SNHL with or without vertigo and often is associated with congenital inner ear abnormalities. Middle-ear exploration may be required to confirm this diagnosis, because no reliable nonoperative diagnostic test exists. It may be necessary to repair a perilymphatic fistula to prevent possible spread of infection from the middle ear to the labyrinth, to stabilize hearing loss, and to improve vertigo when present.

CONGENITAL CHOLESTEATOMA
A congenital cholesteatoma (approximately 2% of all cholesteatomas) is a nonneoplastic, destructive, cystic lesion that usually appears as a white, round, cyst-like structure medial to an intact TM. Cysts are seen most commonly in the anterior-superior portion of the middle ear, although they can present in other locations and within the TM or in the skin of the ear canal. Affected children often have no prior history of otitis media. One theory for the pathogenesis is that the cyst derives from a congenital rest of epithelial tissue that persists beyond 33 wk of gestation, when it ordinarily would disappear. Other theories include squamous metaplasia of the middle ear, entrance of squamous epithelium through a nonintact eardrum into the middle ear, ectodermal implants between the first and second branchial arch remnants, and residual amniotic fluid squamous debris. Congenital or acquired cholesteatoma should be suspected when deep retraction pockets, keratin debris, chronic drainage, aural granulation tissue, or a mass behind or involving the TM is present. Besides acting as a benign tumor causing local bone destruction, the keratinaceous debris of a cholesteatoma is a good culture medium and may become a focus of infection for chronic otitis media. Complications include ossicular erosion with hearing loss, bone erosion into the inner ear with dizziness, or exposure of the dura, with consequent meningitis or a brain abscess. Cholesteatoma should be removed surgically after CT scan (Fig. 638-2) and hearing evaluation, and appropriate antibiotic therapy. A second-look procedure 6-9 mo after primary surgery is often recommended to prevent further recurrence. Higher initial stage of disease, erosion of ossicles, cholesteatoma abutting or enveloping the incus or stapes, and need for removal of the ossicles are associated with increased likelihood of residual cholesteatoma. In addition, more extensive disease at initial surgery is associated with poorer hearing outcomes. Recurrence rates vary and are related to the extent of involvement at the time of surgery. In a large case series, recurrence rates were found to be as follows: 14% when disease was confined to 1 quadrant, 33% when more than 1 quadrant was involved but the ossicles and mastoids were not, 41% with ossicular involvement, and 67% with mastoid involvement. Overall recurrence may be as high as 57%. Congenital cholesteatoma is an aggressive disease, and early surgical
Figure 638-2 Congenital cholesteatoma. Axial CT of left ear shows soft tissue mass (arrow) in the middle ear. This mass was noted otoscopically behind an intact membrane. (From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 44-31, p. 598.)

removal and close monitoring will help prevent permanent damage to the middle and inner ear.

Bibliography is available at Expert Consult.
Bibliography


In an infant, the outer two thirds of the ear canal is cartilaginous and the inner one third is bony. In an older child and adult the outer one third is cartilaginous and the inner two thirds is bony. The epithelium is thinner in the bony portion than in the cartilaginous portion, there is no subcutaneous tissue, and epithelium is tightly applied to the underlying periosteum; hair follicles, sebaceous glands, and apocrine glands are scarce or absent. The skin in the cartilaginous area has well-developed dermis and subcutaneous tissue and contains hair follicles, sebaceous glands, and apocrine glands. The highly viscous secretions of the sebaceous glands and the watery, pigmented secretions of the apocrine glands in the outer portion of the canal combine with exfoliated surface cells of the skin to form cerumen, a protective, waxy, water-repellent coating.

The normal flora of the external canal consists mainly of aerobic bacteria and includes coagulase-negative staphylococci (see Chapter 181.3), Corynebacterium (diphtheroids) (see Chapter 187), Micrococcus, and, occasionally, Staphylococcus aureus (see Chapter 181.1), viridans streptococci (see Chapter 185), and Pseudomonas aeruginosa (see Chapter 205.1). Excessive wetness (swimming, bathing, increased environmental humidity), dryness (dry canal skin and lack of cerumen), the presence of other skin pathologic conditions (previous infection, eczema, or other forms of dermatitis), and trauma (due to digital or foreign body, use of cotton-tip applicators [Q-tips]) make the skin of the canal vulnerable to infection by the normal flora or exogenous bacteria.

ETIOLOGY
External otitis (swimmer’s ear, although it can occur without swimming) is caused most commonly by P. aeruginosa, but S. aureus, Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae, streptococci, coagulase-negative staphylococci, diphtheroids, and fungi such as Candida and Aspergillus also may be isolated. External otitis results from chronic irritation and maceration from excessive moisture in the canal. The loss of protective cerumen may play a role, as may trauma, but cerumen impaction with trapping of water also can cause infection. Inflammation of the ear canal due to herpesvirus, varicella-zoster virus, other skin exanthems, and eczema also may predispose to external otitis.

CLINICAL MANIFESTATIONS
The predominant symptom is acute rapid onset of ear pain (otalgia), often severe, accentuated by manipulation of the pinna or by pressure on the tragus and by jaw motion. The severity of the pain and tenderness (tragus or pinna, or both) may be disproportionate to the degree of inflammation, because the skin of the external ear canal is tightly adhered to the underlying perichondrium and periosteum. Itching often is a precursor of pain and usually is characteristic of chronic inflammation of the canal or resolving acute otitis externa. Conductive hearing loss (CHL) may result from edema of the skin and tympanic membrane (TM), serous or purulent secretions, or the canal skin thickening associated with chronic external otitis.

Edema of the ear canal, erythema, and thick, clammy otorrhea are prominent signs of the acute disease. The cerumen usually is white and soft in consistency, as opposed to its usual yellow color and firmer consistency. The canal often is so tender and swollen that the entire ear canal and TM cannot be adequately visualized, and complete otoscopic examination may be delayed until the acute swelling subsides. If the TM can be visualized, it may appear either normal or opaque. TM mobility may be normal or, if the TM is thickened, mobility may be reduced in response to positive and negative pressure.

Other physical findings may include palpable and tender lymph nodes in the periauricular region, and erythema and swelling of the pinna and periauricular skin. Rarely, facial paralysis, other cranial nerve abnormalities, vertigo, and/or sensorineural hearing loss are present. If these occur, necrotizing (malignant) otitis externa is probable. This invasive infection of the temporal bone and skull base requires immediate culture, intravenous antibiotics, and imaging studies to evaluate the extent of the disease. Surgical intervention to obtain cultures or debride devitalized tissue may be necessary. P. aeruginosa (see Chapter 205.1) is the most common causative organism of necrotizing otitis externa. Fortunately, this disease is rare in children and is seen only in association with immunocompromise or severe malnourishment. In adults, it is associated with diabetes mellitus.

DIAGNOSIS
Diffuse external otitis may be confused with furunculosis, otitis media (OM), and mastoiditis. Furuncles occur in the lateral hair-bearing part of the ear canal; furunculosis usually causes a localized swelling of the canal limited to 1 quadrant, whereas external otitis is associated with concentric swelling and involves the entire ear canal. In OM, the TM may be perforated, severely retracted, or bulging and immobile; hearing usually is impaired. If the middle ear is draining through a perforated TM or tympanostomy tube, secondary external otitis may occur; if the TM is not visible owing to drainage or ear canal swelling, it may be difficult to distinguish acute OM with drainage from an acute external otitis. Pain on manipulation of the auricle and significant lymphadenitis is not common features of OM, and these findings assist in the differential diagnosis. In some patients with external otitis, the periauricular edema is so extensive that the auricle is pushed forward, creating a condition that may be confused with acute mastoiditis and a subperiosteal abscess. In mastoiditis, the postauricular fold is obliterated, whereas in external otitis, the fold is usually
better preserved. In acute mastoiditis, a history of OM and hearing loss is usual; tenderness is noted over the mastoid and not on movement of the auricle; and otoscopic examination may show sagging of the posterior canal wall.

Referred otalgia may come from disease in the paranasal sinuses, teeth, pharynx, parotid gland, neck and thyroid, and cranial nerves (trigeminal neuralgia) (herpes simplex virus, varicella-zoster virus).

**TREATMENT**

Topical otic preparations containing acetic acid with or without hydrocortisone, or neomycin (active against Gram-positive organisms and some Gram-negative organisms, notably *Proteus* spp.), polymyxin (active against Gram-negative bacilli, notably *Pseudomonas* spp.), and hydrocortisone are highly effective in treating most forms of acute external otitis. Other preparations of eardrops (e.g., ofloxacin, ciprofloxacin with hydrocortisone or dexamethasone) are preferable and do not contain potentially ototoxic antibiotics. If canal edema is marked, the patient may need referral to a specialist for cleaning and possible wick placement. An otic antibiotic and corticosteroid eardrop is often recommended. A wick can be inserted into the ear canal and topical antibiotics applied to the wick 3 times a day for 24-48 hr. The wick can be removed after 2-3 days, at which time the edema of the ear canal usually is markedly improved, and the ear canal and TM are better seen. Topical antibiotics are then continued by direct instillation. When the pain is severe, oral analgesics (e.g., ibuprofen, codeine) may be necessary for a few days. Careful evaluation for underlying conditions should be undertaken in patients with severe or recurrent otitis externa. Figure 639-1 outlines an approach to managing acute external otitis.

As the inflammatory process subsides, cleaning the canal with a suction or cotton-tipped applicator to remove the debris enhances the effectiveness of the topical medications. In subacute and chronic infections, periodic cleansing of the canal is essential. In severe, acute external otitis associated with fever and lymphadenitis, oral or parenteral antibiotics may be indicated; an ear canal culture should be done, and empirical antibiotic treatment can then be modified if necessary, based on susceptibility of the organism cultured. A fungal infection of the external auditory canal, or *otomycosis*, is characterized by fluffy white debris, sometimes with black spores seen; treatment includes cleaning and application of antifungal solutions such as clotrimazole or nystatin; other antifungal agents include m-cresyl acetate 25%, gentian violet 2%, and thimerosal 1:1,000.

**PREVENTION**

Preventing external otitis may be necessary for individuals susceptible to recurrences, especially children who swim. The most effective prophylaxis is instillation of dilute alcohol or acetic acid (2%) immediately after swimming or bathing. During an acute episode of otitis externa, patients should not swim and the ears should be protected from excessive water during bathing. A hair dryer may be used to clear moisture from the ear after swimming as a method of prevention.

**OTHER DISEASES OF THE EXTERNAL EAR**

**Furunculosis**

Furunculosis is caused by *S. aureus* and affects only the hair-containing outer third of the ear canal. Mild forms are treated with oral antibiotics active against *S. aureus*. If an abscess develops, incision and drainage may be necessary.
Acute Cellulitis
Acute cellulitis of the auricle and external auditory canal usually is caused by group A streptococcus and occasionally by S. aureus. The skin is red, hot, and indurated, without a sharply defined border. Fever may be present with little or no exudate in the canal. Parenteral administration of penicillin G or a penicillinase-resistant penicillin is the therapy of choice.

Perichondritis and Chondritis
Perichondritis is an infection involving the skin and perichondrium of the auricular cartilage; extension of infection to the cartilage is termed chondritis. The ear canal, especially the lateral aspect, also may be involved. Early perichondritis may be difficult to differentiate from cellulitis because both are characterized by skin that is red, edematous, and tender. The main cause of perichondritis/chondritis and cellulitis is trauma (accidental or iatrogenic, laceration or contusion), including ear piercing, especially when done through the cartilage. The most commonly isolated organism in perichondritis and chondritis is P. aeruginosa, although other Gram-negative and, occasionally, Gram-positive organisms may be found. Treatment involves systemic, often parenteral, antibiotics; surgery to drain an abscess or remove nonviable skin or cartilage may also be needed. Removal of all ear jewelry is mandatory in the presence of infection.

Dermatoses
Various dermatoses (seborrheic, contact, infectious eczematoid, or neurodermatoid) are common causes of inflammation of the external canal; scratching and the introduction of infecting organisms cause acute external otitis in these conditions.

Seborrheic dermatitis is characterized by greasy scales that flake and crumble as they are detached from the epidermis; associated changes in the scalp, forehead, cheeks, brow, postauricular areas, and concha are usual.

Contact dermatitis of the auricle or canal may be caused by earrings or by topical otic medications such as neomycin, which may produce erythema, vesiculation, edema, and weeping. Poison ivy, oak, and sumac also may produce contact dermatitis. Hair care products have been implicated in sensitive individuals.

Infectious eczematoid dermatitis is caused by a purulent infection of the external canal, middle ear, or mastoid; the purulent drainage infects the skin of the canal or auricle, or both. The lesion is weeping, erythematous, or crusted.

Atopic dermatitis occurs in children with a familial or personal history of allergy; the auricle, particularly the postauricular fold, becomes thickened, scaly, and excoriated.

Neurodermatitis is recognized by intense itching and erythematous, thickened epidermis localized to the concha and orifice of the meatus.

Treatment of these dermatoses depends on the type but should include application of an appropriate topical medication, elimination of the source of infection or contact when identified, and management of any underlying dermatologic problem. In addition to topical antibiotics (or antifungals), topical steroids are helpful if contact dermatitis, atopic dermatitis, or eczematoid dermatitis is suspected.

Herpes Simplex Virus
See Chapter 252.

Herpes simplex virus may appear as vesicles on the auricle and lips. The lesions eventually become encrusted and dry and may be confused with impetigo. Topical application of a 10% solution of carbamide peroxide in anhydrous glycerol is symptomatically helpful. The Ramsay Hunt syndrome (herpes zoster oticus with facial paralysis) may present with herpes vesicles in the ear canal and on the pinna and with facial paralysis and pain. Other cranial nerves may be affected as well, especially the 8th nerve. The current recommended treatment of herpes zoster oticus includes systemic antiviral agents, such as acyclovir, and corticosteroids. As many as 50% of patients with Ramsay Hunt syndrome do not completely recover their facial nerve function.

Bullous Myringitis
Commonly associated with an acute upper respiratory tract infection, bullous myringitis presents as an ear infection with more severe pain than usual. On examination, hemorrhagic or serous blisters (bullae) may be seen on the TM. The disease sometimes is difficult to differentiate from acute OM, because a large bulla may be confused with a bulging TM. The organisms involved are the same as those that cause acute OM, including both bacteria and viruses. Treatment consists of empiric antibiotic therapy and pain medications. In addition to ibuprofen or codeine for severe pain, a topical anesthetic eardrop may also provide some relief. Incision of the bullae, although not necessary, promptly relieves the pain.

Exostoses and Osteomas
Exostoses represent benign hyperplasia of the perichondrium and underlying bone. Those involving the auditory canal tend to be found in people who swim often in cold water. Exostoses are broad based, often multiple, and bilateral. Osteomas are benign bony growths in the ear canal of uncertain cause (see Chapter 501.2). They usually are solitary and attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line. Both are more common in males; exostoses are more common than osteomas. Surgical treatment is recommended when large masses cause cerumen impaction, ear canal obstruction, or hearing loss.

Bibliography is available at Expert Consult.
Bibliography
The term otitis media (OM) has 2 main categories: acute infection, which is termed suppurative or acute otitis media (AOM), and inflammation accompanied by middle-ear effusion (MEE), termed nonsuppurative or secretory OM, or otitis media with effusion (OME). These 2 main types of OM are interrelated: acute infection usually is succeeded by residual inflammation and effusion that, in turn, predispose children to recurrent infection. MEE is a feature of both AOM and of OME and is an expression of the underlying middle-ear mucosal inflammation. MEE results in the conductive hearing loss (CHL) associated with OM, ranging from none to as much as 50 dB of hearing loss.

The peak incidence and prevalence of OM is during the 1st 2 yr of life. More than 80% of children will have experienced at least 1 episode of OM by the age of 3 yr. OM is a leading reason for physician visits and for use of antibiotics and figures importantly in the differential diagnosis of fever. OM often serves as the sole or the main basis for undertaking the most frequently performed operations in infants and young children: myringotomy with insertion of tympanostomy tubes and adenoidectomy. OM is also the most common cause of hearing loss in children. OM has a propensity to become chronic and recur. The earlier in life a child experiences the first episode, the greater the degree of subsequent difficulty the child is likely to experience in terms of frequency of recurrence, severity, and persistence of middle-ear effusion.

Accurate diagnosis of AOM in infants and young children may be difficult (Table 640-1). Symptoms may not be apparent, especially in early infancy and in chronic stages of the disease. Accurate visualization of the tympanic membrane and middle-ear space may be difficult because of anatomy, patient cooperation, or blockage by cerumen, removal of which may be arduous and time consuming. Abnormalities of the eardrum may be subtle and difficult to appreciate. In the face of these difficulties, both underdiagnosis and overdiagnosis occur.
Table 640-1 | Treatments for Otalgia in Acute Otitis Media

<table>
<thead>
<tr>
<th>TREATMENT MODALITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen, ibuprofen</td>
<td>Effective analgesia for mild to moderate pain. Readily available. Mainstay of pain management for AOM</td>
</tr>
<tr>
<td>Home remedies (no controlled studies that directly address effectiveness)</td>
<td>May have limited effectiveness</td>
</tr>
<tr>
<td>Distraction</td>
<td></td>
</tr>
<tr>
<td>External application of heat or cold</td>
<td></td>
</tr>
<tr>
<td>Oil drops in external auditory canal</td>
<td></td>
</tr>
<tr>
<td>Benzocaine, procaine, lidocaine (topical)</td>
<td>Additional, but brief, benefit over acetaminophen in patients older than 5 yr</td>
</tr>
<tr>
<td>Naturopathic agents</td>
<td>Comparable to amethocaine/phenazone drops in patients older than 6 yr</td>
</tr>
<tr>
<td>Homeopathic agents</td>
<td>No controlled studies that directly address pain</td>
</tr>
<tr>
<td>Narcotic analgesia with codeine or analogs</td>
<td>Effective for moderate or severe pain. Requires prescription; risk of respiratory depression, altered mental status, gastrointestinal tract upset, and constipation</td>
</tr>
<tr>
<td>Tymanostomy/myringotomy</td>
<td>Requires skill and entails potential risk</td>
</tr>
</tbody>
</table>


**Epidemiology**

Several factors have been demonstrated to affect the occurrence of OM, including age, gender, race, genetic background, socioeconomic status, breast milk feeding, degree of exposure to tobacco smoke, degree of exposure to other children, presence or absence of respiratory allergy, season of the year, and vaccination status. Children with certain types of congenital craniofacial anomalies are particularly prone to OM.

**Age**

The age of onset of OM is an important predictor of the development of recurrent and chronic OM, with earlier age of onset having an increased risk for exhibiting these difficulties later in life. The development of at least 1 episode of OM has been reported as 63-85% by 12 mo and 66-99% by 24 mo of age. The percentage of days with MEE has been reported as 5-27% during the 1st yr of life and 6-18% during the 2nd yr of life. Across groups, rates were highest at 6-20 mo of age. After the age of 2 yr, the incidence and prevalence of OM decline progressively, although the disease remains relatively common into the early school-age years. The most likely reasons for the higher rates in infants and younger children include less-well-developed immunologic defenses and less-favorable eustachian tubal factors involving both the structure and function of the tube.

**Gender**

Epidemiologic data suggest an incidence of OM greater in boys than in girls, although some studies have found no gender-related differences in the occurrence of OM.

**Race**

OM is especially prevalent and severe among Native American, Inuit, and indigenous Australian children. Studies comparing the occurrence of OM in white children and black children have given conflicting results.

**Genetic Background**

That middle-ear disease tends to run in families is a commonplace observation, suggesting that OM has a heritable component. The degree of concordance for the occurrence of OM is much greater among monozygotic than among dizygotic twins.

**Socioeconomic Status**

Poverty has long been considered an important contributing factor to both the development and the severity of OM. Elements contributing to this relationship include crowding, limited hygienic facilities, suboptimal nutritional status, limited access to medical care, and limited resources for complying with prescribed medical regimens.

**Breast Milk Compared to Formula Feeding**

Most studies have found a protective effect of breast milk feeding against OM. This protective effect may be greater in socioeconomically disadvantaged than in more advantaged children. The protective effect is attributable to the milk itself rather than to the mechanics of breastfeeding.

**Exposure to Tobacco Smoke**

Exposure to tobacco smoke is thought to be an important preventable risk factor in the development of OM. Studies that have used objective measures to determine infant exposure to second-hand tobacco smoke, such as cotinine levels, have more consistently identified a significant linkage between tobacco smoke and OM.

**Exposure to Other Children**

Many studies have established that a strong, positive relationship exists between the occurrence of OM and the extent of repeated exposure to other children—measured mainly by the number of other children involved—whether at home or in out-of-home group daycare. Together, but independently, family socioeconomic status and the extent of exposure to other children appear to constitute 2 of the most important identifiable risk factors for developing OM.

**Season**

In keeping with the pattern of occurrence of upper respiratory tract infections in general, highest rates of occurrence of OM are observed during cold weather months and lowest rates during warm weather months. In OM, it is likely that these findings strongly depend on the significant association of OM with viral respiratory illnesses.

**Congenital Anomalies**

OM is universal among infants with unrepaired palatal clefts, and is also highly prevalent among children with submucous cleft palate, other craniofacial anomalies, and Down syndrome (see Chapter 81.2). The common feature in these congenital anomalies is a deficiency in the functioning of the eustachian tubes, which predisposes these children to middle-ear disease.

**Vaccination Status**

See “Immunoprophylaxis” below.
Other Factors

Pacificer use is linked with an increased incidence of OM and recurrence of OM, although the effect is small. Neither maternal age nor birthweight nor season of birth appears to influence the occurrence of OM once other demographic factors are taken into account. Very limited data are available regarding the association of OM with bottle feeding in the recumbent position.

ETIOLOGY

Acute Otitis Media

Pathogenic bacteria can be isolated by standard culture techniques from middle-ear fluid in a majority of well-documented AOM cases. Three pathogens predominate in AOM: Streptococcus pneumoniae (see Chapter 182), nontypeable Haemophilus influenzae (see Chapter 194), and Moraxella catarrhalis (see Chapter 196). The overall incidence of these organisms has changed with the use of the conjugate pneumococcal vaccine. In countries where this vaccine is employed, nontypeable H. influenzae initially overtook S. pneumoniae as the most common pathogen, being found in 40-50% of cases. However, over time, S. pneumoniae serotypes not covered in the conjugate vaccine have emerged, with S. pneumoniae again overtaking nontypeable H. influenzae as the most common pathogen in many studies. M. catarrhalis represents the majority of the remaining cases. Other pathogens include group A streptococcus (see Chapter 183), Staphylococcus aureus (see Chapter 181), and Gram-negative organisms. S. aureus and Gram-negative organisms are found most commonly in neonates and very young infants who are hospitalized; in outpatient settings, the distribution of pathogens in these young infants is similar to that in older infants. Molecular techniques to identify nonculturable bacterial pathogens have suggested the importance of other bacterial species such as Alloiococcus otitidis.

Evidence of respiratory viruses also may be found in middle-ear exudates of children with AOM, either alone or, more commonly, in association with pathogenic bacteria. Of these viruses, rhinovirus and respiratory syncytial virus are found most often. AOM is a known complication of bronchiolitis; middle-ear aspirates in children with bronchiolitis regularly contain bacterial pathogens, suggesting that respiratory syncytial virus is rarely, if ever, the sole cause of their AOM. Using more precise measures of viable bacteria than standard culture techniques, such as polymerase chain reaction assays, a much higher rate of bacterial pathogens can be demonstrated. It remains uncertain whether viruses alone can cause AOM, or whether their role is limited to setting the stage for bacterial invasion, and perhaps also to amplifying the inflammatory process and interfering with resolution of the bacterial infection. Viral pathogens have a negative impact on eustachian tube function, can impair local immune function, and increase bacterial adherence, and can change the pharmacokinetic dynamics, reducing the efficacy of antimicrobial medications.

Otitis Media with Effusion

Using standard culture techniques, the pathogens typically found in AOM are recoverable in only 30% of children with OME. However, in studies of children with OME using polymerase chain reaction assays, middle-ear effusions have been found to contain evidence of bacterial DNA and viral RNA in much larger proportions of these children. These studies suggest that these patients do not have sterile effusions as previously thought. Biofilms of pathogenic bacteria have been demonstrated to be present on the middle-ear mucosa and adenoid pad in a majority of children with chronic OM. Biofilms consist of aggregated and adherent bacteria, embedded in an extracellular matrix, allowing for protection against antimicrobials, and their presence may contribute to the persistence of pathogens and the recalcitrance of chronic OM to antibiotic treatment (see Chapter 171).

PATHOGENESIS

A multifactorial disease process, risk profile, and host–pathogen interactions have become recognized as playing important roles in the pathogenesis of OM. Such events as alterations in mucociliary clearance through repeated viral exposure experienced in daycare settings or through exposure to tobacco smoke may tip the balance of pathogenesis in less-virulent OM pathogens in their favor, especially in children with a unique host predisposition.

Anatomic Factors

Patients with significant craniofacial abnormalities affecting the eustachian tube function have an increased incidence of OM. During the pathogenesis of OM the eustachian tube demonstrates decreased effectiveness in ventilating the middle-ear space. Under usual circumstances the eustachian tube is passively closed and is opened by contraction of the tensor veli palatini muscle. In relation to the middle ear, the tube has 3 main functions: ventilation, protection, and clearance. The middle-ear mucosa depends on a continuing supply of air from the nasopharynx delivered by way of the eustachian tube. Interruption of this ventilatory process by tubal obstruction initiates an inflammatory response that includes secretory metaplasia, compromise of the mucociliary transport system, and effusion of liquid into the tympanic cavity. Measurements of eustachian tube function have demonstrated that the tubal function is suboptimal during the events of OM with increased opening pressures.

Eustachian tube obstruction may result from extraluminal blockage via hypertrophied nasopharyngeal adenoid tissue or tumor, or may result from intraluminal obstruction via inflammatory edema of the tubal mucosa, most commonly as a consequence of a viral upper respiratory tract infection. Progressive reduction in tubal wall compliance with increasing age may explain the progressive decline in the occurrence of OM as children grow older. The protection and clearance functions of the eustachian tube may also be involved in the pathogenesis of OM. Thus, if the eustachian tube is patulous or excessively compliant, it may fail to protect the middle ear from reflux of infective nasopharyngeal secretions, whereas impairment of the mucociliary clearance function of the tube might contribute to both the establishment and persistence of infection. The shorter and more horizontal orientation of the tube in infants and young children may increase the likelihood of reflux from the nasopharynx and impair passive gravitational drainage through the eustachian tube.

In special patient populations with craniofacial abnormalities there exists an increased incidence of OM that has been associated with the abnormal eustachian tube function. In children with cleft palate, where OM is a universal finding, a main factor underlying the chronic middle-ear inflammation appears to be impairment of the opening mechanism of the eustachian tube. Possible factors include muscular changes, tubal compliance factors, and defective velopharyngeal valving, which may result in disturbed aerodynamic and hydrodynamic relationships in the nasopharynx and proximal portions of the eustachian tubes. In children with other craniofacial anomalies and with Down syndrome, the high prevalence of OM has also been attributed to structural and/or functional eustachian tubal abnormalities.

Host Factors

The effectiveness of a child’s immune system in response to the bacterial and viral insults of the upper airway and middle ear during early childhood probably is the most important factor in determining which children are otitis prone. The maturation of this immune system during early childhood is most likely the primary event leading to the decrease in incidence of OM as children move through childhood. Immunglobulin (Ig) A deficiency is found in some children with recurrent AOM, but the significance is questionable, inasmuch as IgA deficiency is also found not infrequently in children without recurrent AOM. Selective IgG subclass deficiencies (despite normal total serum IgG) may be found in children with recurrent AOM in association with recurrent sinopulmonary infection, and these deficiencies probably underlie the susceptibility to infection. Children with HIV infection have recurrent and difficult to treat episodes of AOM in the 1st and 2nd yr of life. Children with recurrent OM that is not associated with recurrent infection at other sites rarely have a readily identifiable immunologic deficiency. Evidence that subtle immune deficits play a role in the pathogenesis of recurrent AOM is provided by studies involving antibody responses to various types of infection and
imunization; by the observation that breast milk feeding, as opposed to formula feeding, confers some protection against the occurrence of OM in infants with cleft palate; and by studies in which young children with recurrent AOM achieved a measure of protection from intramuscularly administered bacterial polysaccharide immune globulin or intravenously administered polyclonal immunoglobulin. This evidence, along with the documented decrease in incidence of upper respiratory tract infections and OM as children’s immune systems develop and mature, is indicative of the importance of a child’s innate immune system in the pathogenesis of OM (see Chapter 124).

Viral Pathogens

Although OM may develop and certainly may persist in the absence of apparent respiratory tract infection, many, if not most, episodes are initiated by viral or bacterial upper respiratory tract infection. In children in group daycare, AOM was observed in approximately 30–40% of children with respiratory illness caused by respiratory syncytial virus (see Chapter 260), influenza viruses (see Chapter 258), or adenoviruses (see Chapter 262), and in approximately 10–15% of children with respiratory illness caused by parainfluenza viruses (see Chapter 259), rhinoviruses (see Chapter 263), or enteroviruses (see Chapter 250). Viral infection of the upper respiratory tract results in release of cytokines and inflammatory mediators, some of which may cause eustachian tube dysfunction.

Respiratory viruses also may enhance nasopharyngeal bacterial colonization and adherence and impair host immune defenses against bacterial infection.

Allergy

Evidence that respiratory allergy is a primary etiologic agent in OM is not convincing; however, in children with both conditions it is possible that the otitis is aggravated by the allergy.

CLINICAL MANIFESTATIONS

Symptoms of AOM are variable, especially in infants and young children. In young children, evidence of ear pain may be manifested by irritability or a change in sleeping or eating habits and occasionally, rubbing of the ear. Pulling at the ear alone has a low sensitivity and specificity. Fever may also be present and may occasionally be the only sign. Rupture of the tympanic membrane with purulent otorrhea is uncommon. Systemic symptoms and symptoms associated with upper respiratory tract infections also occur; occasionally there may be no symptoms, the disease having been discovered at a routine health examination. OM often is not accompanied by overt complaints of the child but can be accompanied by hearing loss. This hearing loss may manifest as changes in speech patterns but often goes undetected if unilateral or mild in nature, especially in younger children. Balance difficulties or disequilibrium can also be associated with OME and older children may complain of mild discomfort or a sense of fullness in the ear (see Chapter 636).

EXAMINATION OF THE TYPANIC MEMBRANE

Otoscopy

Two types of otoscope heads are available: surgical or operating, and diagnostic or pneumatic. The surgical head embodies a lens that can swivel over a wide arc and an unenclosed light source, thus providing ready access of the examiner’s instruments to the external auditory canal and tympanic membrane. Use of the surgical head is optimal for removing cerumen or debris from the canal under direct observation, and is necessary for satisfactorily performing tympanocentesis or myringotomy. The diagnostic head incorporates a larger lens, an enclosed light source, and a nipple for the attachment of a rubber bulb and tubing. When an attached speculum is fitted snugly into the external auditory canal, an airtight chamber is created comprising the vault of the otoscope head, the bulb and tubing, the speculum, and the proximal portion of the external canal. Although examination of the ear in young children is a relatively invasive procedure that is often met with lack of cooperation by the patient, this task can be enhanced if done with as little pain as possible. The outer portion of the ear canal contains hair-bearing skin and subcutaneous fat and cartilage that allow a speculum to be placed with relatively little discomfort. Closer to the tympanic membrane the ear canal is made of bone and is lined only with skin and no adnexal structures or subcutaneous fat; a speculum pushed too far forward and placed in this area often causes skin abrasion and pain. Using a rubber-tipped speculum or adding a small sleeve of rubber tubing to the tip of the plastic speculum may serve to minimize patient discomfort and enhance the ability to achieve a proper fit and an airtight seal, facilitating pneumatic otoscopy.

Learning to perform pneumatic otoscopy is a critical skill in being able to assess a child’s ear and in making an accurate diagnosis of AOM. By observing as the bulb is alternately squeezed gently and released, the degree of tympanic membrane mobility in response to both positive and negative pressure can be estimated, providing a critical assessment of middle-ear fluid, which is a hallmark sign of both AOM and OME (Fig. 640–1). With both types of otoscope heads, bright illumination is also critical for adequate visualization of the tympanic membrane.

Clearing the External Auditory Canal

Many children’s ears are “self-cleaning” because of squamous migration of ear canal skin. Parental cleaning of cerumen with cotton swabs often complicates cerumen impaction by pushing cerumen deeper into the canal compacting it. If the tympanic membrane is obscured by cerumen, the cerumen should be removed. This can be accomplished through
direct visualization using a headlight or through the surgical head of the otoscope by using an ear curette or gentle suction with a No. 5 or 7 French ear suction tube. During this procedure it may be most advantageous to restrain the infant or young child in the prone position, turning the child's head to the left or right as each ear is cleared. In children old enough to cooperate, usually beginning at about 3 yr of age, clearing of the external canal may be achieved more easily and less traumatically by lavage than by mechanical removal, provided one can be certain that a tympanic membrane perforation is not present.

**Tympanic Membrane Findings**

Important characteristics of the tympanic membrane (TM) consist of contour, color, translucence, structural changes if any, and mobility. The TM is anatomically divided into the pars tensa and pars flaccida. The pars tensa comprises the lower two thirds of the drum inferior to the lateral process of the malleus. Its contour is normally slightly concave; abnormalities consist of fullness or bulging or, conversely, extreme retraction. The normal color of the pars tensa is pearly gray, with the pars flaccida being slightly more vascular in nature. Erythema may be a sign of inflammation or infection, but unless intense, erythema alone may result from crying or vascular flushing. Abnormal whiteness of the membrane may result from either scarring or the presence of effusion in the middle-ear cavity; this effusion also may impart an amber, pale yellow, or, rarely, bluish color. Rarely a persistent focal white area may be indicative of a congenital cholesteatoma in the middle-ear space. Normally, the membrane is translucent, although some degree of opacity may be normal in the 1st few mo of life; later, opacification denotes either scarring or, more commonly, underlying effusion. Structural changes include scars, perforations, and retraction pockets. Retractions or perforations, especially in the posterior-superior quadrant, or pars flaccida, of the TM may be a sign of cholesteatoma formation. Of all the visible characteristics of the TM, mobility is the most sensitive and specific in determining the presence or absence of MEE. Mobility is generally not an all-or-none phenomenon. A total absence of mobility does exist with a TM perforation that can develop following a substantial increase in middle-ear pressure associated with effusion. When a perforation is not present, substantial impairment of mobility is the more common finding with MEE. Bulging of the TM is the most specific finding of AOM (97%) but has lower specificity (51%) (Fig. 640-2).

**Diagnosis**

The 2013 guidelines from the American Academy of Pediatrics for diagnosis of AOM are more restrictive than were the earlier (2004) guidelines. The 2004 guidelines employed a 3-part definition: (1) acute onset of symptoms; (2) presence of an MEE; and (3) signs of acute middle-ear inflammation. This definition was thought by the 2013 American Academy of Pediatrics to lack sufficient precision and thereby liable to include cases of OME and/or enable the diagnosis of AOM to be made without visualizing the TM.

A diagnosis of AOM according to the 2013 guideline should be made in children who present with:

- moderate to severe bulging of the TM or new-onset otorrhea not caused by otitis externa
- mild bulging of the TM and recent (<48 hr) onset of ear pain or intense TM erythema

A diagnosis of OAM should not be made in children without MEE. AOM and OME may evolve into the other without any clearly differentiating physical findings; any schema for distinguishing between them is to some extent arbitrary. In an era of increasing bacterial resistance, distinguishing between AOM and OME is important in determining treatment, because OME in the absence of acute infection does not require antimicrobial therapy. Purulent otorrhea of recent onset is indicative of AOM; thus, difficulty in distinguishing clinically between AOM and OME is limited to circumstances in which purulent otorrhea is not present. Both AOM without otorrhea and OME are accompanied by physical signs of MEE, namely, the presence of at least 2 of 3 TM abnormalities: white, yellow, amber, or (rarely) blue discoloration; opacification other than that caused by scarring; and increased or absent mobility. Alternatively in OME, either air–fluid levels or air bubbles outlined by small amounts of fluid may be visible behind the TM, a condition often indicative of impending resolution (Fig. 640-3).

To support a diagnosis of AOM instead of OME in a child with MEE, distinct fullness or bulging of the TM may be present, with or without accompanying erythema, or, at a minimum, MEE should be accompanied by ear pain that appears clinically important. Unless intense, erythema alone is insufficient because erythema, without other abnormalities, may result from crying or vascular flushing. In AOM, the malleus may be obscured and the TM may resemble a bagel without a hole but with a central depression (see Fig. 640-3). Rarely, the TM may be obscured by surface bullae or may have a cobblestone appearance. Bullous myringitis is a physical manifestation of AOM and not an etiologically discrete entity. Within days after onset, fullness of the membrane may diminish, even though infection may still be present.

In OME, bulging of the TM is absent or slight or the membrane may be retracted (Fig. 640-4); erythema also is absent or slight, but may increase with crying or with superficial trauma to the external auditory canal incurred in clearing the canal of cerumen.

Both before and after episodes of OM and also in the absence of OM, the TM may be retracted as a consequence of negative middle-ear air pressure. The presumed cause is diffusion of air from the middle-ear cavity more rapidly than it is replaced via the eustachian tube. Mild
retraction is generally self-limited, although in some children it is accompanied by mild conductive hearing loss. More extreme retraction is of concern, as discussed later in the section on sequelae of OM.

**Conjunctivitis-Associated Otitis Media**

Simultaneous appearance of purulent and erythematous conjunctivitis with an ipsilateral OM is a well-recognized presentation, caused by nontypeable *H. influenzae* in most children.

The disease often is present in multiple family members and affects young children and infants. Topical ocular antibiotics are ineffective. In an era of resistant organisms, this clinical association can be important in antibiotic selection, with oral antibiotics (see later) effective against resistant forms of nontypeable *H. influenzae*.

**Asymptomatic Purulent Otitis Media**

Rarely, a child will present during a routine exam without fever, irritability, or other overt signs of infection, but on exam, the patient will demonstrate an obvious purulent MEE and bulging TM. Although an uncommon presentation of “acute” OM, the bulging nature of the TM and the obvious purulence of the effusion do warrant antimicrobial therapy.

**Tympanometry**

Tympanometry, or acoustic immittance testing, is a simple, rapid, atraumatic test that, when performed correctly, offers objective evidence of the presence or absence of MEE. The tympanogram provides information about TM compliance in electroacoustic terms that can be thought of as roughly equivalent to TM mobility as perceived visually during pneumatic otoscopy. The absorption of sound by the TM varies inversely with its stiffness. The stiffness of the membrane is least, and accordingly its compliance is greatest, when the air pressures impinging on each of its surfaces—middle-ear air pressure and external canal air pressure—are equal. In simple terms, anything tending to stiffen the TM, such as TM scarring or middle-ear fluid, reduces the TM compliance, which is recorded as a flattening of the curve of the tympanogram. An ear filled with middle-ear fluid generally has a very noncompliant TM and, therefore, a flattened tympanogram tracing.

*Tympanograms* may be grouped into 1 of 3 categories (Fig. 640-5).

Tracings characterized by a relatively steep gradient, sharp-angled peak, and middle-ear air pressure (location of the peak in terms of air pressure) that approximates atmospheric pressure (Fig. 640-5A) (type A curve) are assumed to indicate normal middle-ear status. Tracings characterized by a shallow peak or no peak are often termed “flat” or type B (Fig. 640-5B), and usually are assumed to indicate the presence of a middle-ear abnormality that is causing decreased TM compliance. The most common such abnormality in infants and children is MEE. Tracings characterized by intermediate findings—somewhat shallow peak, often in association with a gradual gradient (obtuse-angled peak) or negative middle-ear air pressure peak (often termed type “C”), or combinations of these features (Fig. 640-5C)—may or may not be associated with MEE, and must be considered nondiagnostic or equivocal with respect to OM. However, type C tympanograms do suggest eustachian tube dysfunction and some ongoing pathology in the middle ear and warrant follow-up.

When reading a tympanogram it is important to look at the volume measurement. The type B tympanometric response has to be analyzed within the context of the recorded volume. A flat, “low”-volume (<1 mL) tracing typically reflects the volume of the ear canal only, representing MEE, which impedes the movement of an intact ear drum. A flat, high-volume (>1 mL) tracing typically reflects the volume of the ear canal and middle-ear space, representing a perforation (or patent tympanostomy tube) in the TM. In a child with a tympanostomy tube present, a flat tympanogram with a volume <1 mL would suggest a plugged or nonfunctioning tube and middle-ear fluid, whereas a flat tympanogram with a volume >1 mL would suggest a patent tympanostomy tube.

Although tympanometry is quite sensitive in detecting MEE, it can be limited by patient cooperation, the skill of the individual administering the test, and the age of the child, with less-reliable results in very young children. Use of tympanometry may be helpful in office screening, may supplement the examination of difficult to examine patients, and may help identify patients who require further attention because their tympanograms are abnormal. Tympanometry also may be used to help confirm, refine, or clarify questionable otoscopic findings; to objectify the follow-up evaluation of patients with known middle-ear disease; and to validate otoscopic diagnoses of MEE. Even...
though tympanometry can predict the probability of OME from that of AOM.

**PREVENTION**

General measures to prevent OM that have been supported by a number of investigations include avoiding exposure to individuals with respiratory infection; appropriate vaccination strategies against pneumococci and influenzae; avoiding environmental tobacco smoke; and breast milk feeding.

**IMMUNOPROPHYLAXIS**

Heptavalent pneumococcal conjugate vaccine (PCV7) reduced the overall number of episodes of AOM by only 6-8% but with a 57% reduction in serotype-specific episodes. Reductions of 9-23% are seen in children with histories of frequent episodes, and a 20% reduction is seen in the number of children undergoing tympanostomy tube insertion. A 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) was licensed by the FDA in 2010. PCV13 contains the 7 serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A). The effects of PCV13 on AOM incidence reduce pneumococcal nasopharyngeal carriage, including serotypes 19A, 7F, and 6C, in young children (younger than age 2 yr) with AOM. Given that 19A is a particularly invasive pneumococcal serotype, the effect of PCV13 on reducing complicated AOM will hopefully be of significance. Early data indicate a significant reduction in the number of invasive pneumococcal mastoiditis cases since the introduction of PCV13. With the widespread use of PCV13, continued surveillance will be necessary to detect other emerging serotypes, which are also demonstrating increasing resistance. Although the influenza vaccine also provides a measure of protection against OM, the relatively limited time during which individuals and even communities are exposed to influenza viruses limits the vaccine’s effectiveness in broadly reducing the incidence of OM. Limitation of OM disease is only a portion of the benefit realized from the vaccinations for pneumococci and influenza viruses. Support for these vaccination programs requires an understanding of the preventive benefit for OM in concert with the other benefits.

**TREATMENT**

**Management of Acute Otitis Media**

AOM can be very painful. Whether or not antibiotics are employed for treatment, pain should be assessed and if present, treated (see Table 640-1).

Individual episodes of AOM have traditionally been treated with antimicrobial drugs. Concern about increasing bacterial resistance has prompted some clinicians to recommend withholding antimicrobial treatment in some or most cases unless symptoms persist for 2 or 3 days, or worsen (Table 640-2). Three factors argue in favor of routinely prescribing antimicrobial therapy for children who have documented AOM using the diagnostic criteria outlined previously (see “Diagnosis” above). First, pathogenic bacteria cause a large majority of cases. Second, symptomatic improvement and resolution of infection occur more promptly and more consistently with antimicrobial treatment than without, even though most untreated cases eventually resolve. Third, prompt and adequate antimicrobial treatment may prevent the development of suppurative complications. The sharp decline in such complications during the last half-century seems likely attributable, at least in part, to the widespread routine use of antimicrobials for AOM. In the Netherlands, where initial antibiotic treatment is routinely withheld from most children older than 6 mo of age, and where only approximately 30% of children with AOM receive antibiotics at all, the incidence of acute mastoiditis, although low (in children younger than age 14 yr, 3.8 per 100,000 person-years), appears slightly higher than rates in other countries with higher antibiotic prescription rates by about 1-2 episodes per 100,000 person-years. Groups in other countries where initial conservative management of AOM is the standard in children older than 6 mo, such as Denmark, report acute mastoiditis rates similar to those of the Netherlands (4.8 per 100,000 person-years).

Given that most episodes of OM will spontaneously resolve, consensus guidelines have been published by the American Academy of Pediatrics to assist clinicians who wish to consider a period of “watchful waiting” or observation prior to treating AOM with antibiotics (see Tables 640-2 and 640-3; Fig. 640-6). The most important aspect of these guidelines is that close follow-up of the patient must be ensured to assess for lack of spontaneous resolution or worsening of symptoms and that patients should be provided with adequate analgesic medications (acetaminophen, ibuprofen) during the period of observation. When pursuing the practice of watchful waiting in patients with AOM, the certainty of the diagnosis, the patient’s age, and the severity of the disease should be considered. For younger patients, <2 yr of age, it is recommended to treat all confirmed diagnoses of AOM. In very young patients, <6 mo of age, even presumed episodes of AOM should be treated because of the increased potential of significant morbidity from infectious complications. In children between 6 and 24 mo of age who have a questionable diagnosis of OM but severe disease, defined as temperature of >39°C (102.2°F), significant otalgia, or toxic appearance, antibiotic therapy is also recommended. Children in this age group with a questionable diagnosis and nonsevere disease can be observed for a period of 2-3 days with close follow-up. In children older than 2 yr of age, observation might be considered in all episodes of nonsevere OM or episodes of questionable diagnosis, while antibiotic therapy is reserved for confirmed, severe episodes of AOM. Information from Finland suggests that the “watchful waiting” or delayed treatment approach does not worsen the recovery from AOM, or increase the complication rates. However, watchful waiting may be associated with transient worsening of the child’s condition and longer overall duration of symptoms.

Accurate diagnosis is the most crucial aspect of the treatment of OM. In studies utilizing stringent criteria for diagnosis of AOM the benefit of antimicrobial treatment is enhanced. Additionally, subpopulations of patients clearly receive more benefit from oral antimicrobial

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**Table 640-2 Recommendations for Initial Management for Uncomplicated Acute Otitis Media**

<table>
<thead>
<tr>
<th>AGE</th>
<th>OTORRHEA WITH AOM*</th>
<th>UNILATERAL OR BILATERAL AOM* WITH SEVERE SYMPTOMS 1</th>
<th>BILATERAL AOM* WITHOUT OTORRHEA</th>
<th>UNILATERAL AOM* WITHOUT OTORRHEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo to 2 yr</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy or additional observation</td>
</tr>
<tr>
<td>≥2 yr</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy or additional observation</td>
<td>Antibiotic therapy or additional observation</td>
</tr>
</tbody>
</table>

*Applies only to children with well-documented AOM with high certainty of diagnosis.

1A toxic-appearing child, persistent otalgia more than 48 hr, temperature ≥39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.

2This plan of initial management provides an opportunity for shared decision making with the child’s family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.

**NOTE:** For infants younger than age 6 mo, a suspicion of AOM should result in antibiotic therapy.

therapy than others. Younger children, children with otitis media, and children with bilateral AOM have a significantly enhanced benefit from antimicrobial therapy in comparison to older children, children without otitis media, or children with unilateral AOM.

### Bacterial Resistance
Persons at greatest risk of harboring resistant bacteria are those who are younger than 2 yr of age, who are in regular contact with large groups of other children, especially in daycare settings, or who recently have received antimicrobial treatment. Bacterial resistance is a particular problem in relation to OM. The development of resistant bacterial strains and their rapid spread have been fostered and facilitated by selective pressure resulting from extensive use of antimicrobial drugs, the most common target of which, in children, is OM. Many strains of each of the pathogenic bacteria that commonly cause AOM are resistant or susceptible to commonly used antimicrobial drugs.

Although antimicrobial resistance rates vary between countries, in the United States approximately 40% of strains of nontypeable *H. influenzae* and almost all strains of *M. catarrhalis* are resistant to aminopenicillins (e.g., amoxicillin and amoxicillin). In most cases, the resistance is attributable to production of β-lactamase and can be overcome by combining amoxicillin with a β-lactamase inhibitor (clavulanate) or by using β-lactamase–stable antibiotic. Occasional strains of nontypeable *H. influenzae* that do not produce β-lactamase are resistant to aminopenicillins and other β-lactam antibiotics by virtue of alterations in their penicillin-binding proteins. It is worth noting that bacterial resistance rates in northern European countries where antibiotic usage is less are comparatively exceedingly lower (resistance rates in northern European countries where antibiotic usage is less are comparatively exceedingly lower than those in the United States). In children attending daycare, resistance by β-lactam antibiotics is mediated not by β-lactamase production but by alterations in penicillin-binding proteins. This mechanism of resistance can be overcome if higher concentrations of β-lactam antibiotics at the site of infection can be achieved for a sufficient time interval. Many penicillin-resistant strains of *S. pneumoniae* are also resistant to other antimicrobial drugs, including sulfonamides, macrolides, and cefalosporins. In general, as penicillin resistance increases, so also does resistance to other antimicrobial classes. Resistance to macrolides, including azithromycin and clarithromycin, by *S. pneumoniae* has increased rapidly, rendering these antimicrobials far less effective in treating AOM. One mechanism of resistance to macrolides also results in resistance to clindamycin, which otherwise is generally effective against resistant strains of *S. pneumoniae*. Unlike resistance to β-lactam antibiotics, macrolide resistance cannot be overcome by increasing the dose.

### First-Line Antimicrobial Treatment
Amoxicillin remains the drug of first choice for uncomplicated AOM under many circumstances because of its excellent record of safety, relative efficacy, palatability, and low cost. In particular, amoxicillin is the most efficacious of available oral antimicrobial drugs against both penicillin-susceptible and penicillin-nonsusceptible strains of *S. pneumoniae*. Increasing the dose from the traditional 40–45 mg/kg/24 hr to 80–90 mg/kg/24 hr will generally provide efficacy against penicillin-resistant strains and also some clindamycin-resistant strains. This higher dose should be used particularly in children younger than 2 yr of age, in children who have recently received treatment with β-lactam drugs, and in children who are exposed to large numbers of other children because of their increased likelihood of an infection with a nonsusceptible strain of *S. pneumoniae*. A limitation of amoxicillin is that it may be inactivated by the β-lactamases produced by many strains of nontypeable *H. influenzae* and most strains of *M. catarrhalis*. Episodes of AOM caused by these pathogens often resolve spontaneously. Allergies to penicillin antibiotics should be categorized into type I hypersensitivity, consisting of urticaria or anaphylaxis, and those that fall short of type I reactions, such as rash formation. For children with a non–type I reaction in which cross reactivity with cephalosporins is less of a concern, first-line therapy with cefdinir would be an appropriate choice. In children with a type I reaction or known sensitivity to ceftriaxone, other antibiotics should be considered.
Figure 640-6 Management of acute otitis media. (From Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media, Pediatrics 113:1451–1465, 2004.)

trimethoprim-sulfamethoxazole by many strains of both nontypeable H. influenzae and S. pneumoniae and a reported high clinical failure rate in children with AOM treated initially with this antimicrobial argue against its use. Similarly, increasing rates of macrolide resistance argue against the efficacy of azithromycin. Although not approved by the FDA for use in children, many clinicians have employed quinolones in this patient population. Early alternative management in these allergic patients with tympanostomy tubes can allow for lessening of the severity of their disease and the utilization of topical antimicrobials.
Duration of Treatment

The duration of treatment of AOM has historically been set at 10 days and most efficacy studies examining antimicrobial treatment in AOM have utilized this duration as a benchmark. Studies comparing shorter with longer durations of treatment suggest that short-course treatment will often prove inadequate in children younger than 6 yr of age and particularly in children younger than 2 yr of age. Thus, for most episodes in most children, treatment that provides tissue concentrations of an antimicrobial for at least 10 days is advisable. Treatment for longer than 10 days may be required for children who are very young or have been having severe episodes or whose previous experience with OM has been problematic.

Follow-Up

The principal goals of follow-up are to assess the outcome of treatment and “to differentiate between inadequate response to treatment and early recurrence. The appropriate interval for follow-up should be individualized. Follow-up within days is advisable in the young infant with a severe episode or in a child of any age with continuing pain. Follow-up within 2 wk is appropriate for the infant or young child who has been having frequent recurrences. At that point, the TM is not likely to have returned to normal, but substantial improvement in its appearance should be evident. In the child with only a sporadic episode of AOM and prompt symptomatic improvement, follow-up 1 mo after initial examination is early enough, or in older children, no follow-up may be necessary. The continuing presence of MEE alone following an episode of AOM is not an indication for additional or second-line antimicrobial treatment. However, persisting MEE does warrant additional follow-up to ensure that this resolves and does not lead to persisting hearing loss or other complications.

Unsatisfactory Response to First-Line Treatment

AOM is essentially a closed-space infection and its resolution depends both on eradication of the offending organism and restoration of middle-ear ventilation. Factors contributing to unsatisfactory response to first-line treatment, in addition to inadequate antimicrobial efficacy, include poor compliance with treatment regimens; concurrent or intercurrent viral infection; persistent eustachian tube dysfunction and middle-ear underaeration; re-infection from other sites or from incompletely eradicated middle-ear pathogens; and immature or impaired host defenses. The identification of biofilm formation in the middle ear of children with chronic OM also indicates that, in some children, eradication with standard antimicrobial therapy is likely to be unsuccessful. Despite these many potential factors, switching to an alternative or second-line drug is reasonable when there has been inadequate improvement in symptoms or in middle-ear status as reflected in the appearance of the TM, or when the persistence of purulent nasal discharge suggests that the antimicrobial drug being used has less-than-optimal efficacy. Second-line drugs may also appropriately be used when AOM develops in a child already receiving antimicrobial therapy, or in an immunocompromised child, or in a child with severe symptoms whose previous experience with OM has been problematic.

Second-Line Treatment

When treatment of AOM with a first-line antimicrobial drug has proven inadequate, a number of second-line alternatives are available (see Table 640-3). Drugs chosen for second-line treatment should be effective against β-lactamase–producing strains of nontypeable H. influenzae and M. catarrhalis and against susceptible and most non-susceptible strains of S. pneumoniae. Only 4 antimicrobial agents meet these requirements: amoxicillin-clavulanate, cefdinir, cefuroxime axetil, and intramuscular ceftriaxone. Because high-dose amoxicillin (80–90 mg/kg/24 hr) is effective against most strains of S. pneumoniae and because the addition of clavulanate extends the effective antibacterial spectrum of amoxicillin to include β-lactamase–producing bacteria, high-dose amoxicillin-clavulanate is particularly well-suited as a second-line drug for treating AOM. The 14:1 amoxicillin-clavulanate formulation contains twice as much amoxicillin as the previously available 7:1 formulation. Diarrhea, especially in infants and young children, is a common adverse effect, but may be ameliorated in some cases by feeding active culture yogurt, and usually is not severe enough to require cessation of treatment. Cefdinir has demonstrated broad efficacy in treatment, is generally well tolerated with respect to taste, and can be given as a once-daily regimen. The ability to also utilize cefdinir in most children with mild type 1 hypersensitivity reactions has further added to its favorable selection as a second-line agent. Both ceftriaxone axetil and intramuscular ceftriaxone have important limitations for use in young children. The currently available suspension of ceftriaxone axetil is not palatable and its acceptance is low.

Ceftriaxone treatment entails both the pain of intramuscular injection and substantial cost, and the injection may need to be repeated once or twice at 2 day intervals to achieve the desired degree of effectiveness. Nonetheless, use of ceftriaxone is appropriate in severe cases of AOM when oral treatment is not feasible, or in highly selected cases after treatment failure using orally administered second-line antimicrobials (i.e., amoxicillin-clavulanate or cefuroxime axetil), or when highly resistant S. pneumoniae is found in aspirates obtained from diagnostic tympanocentesis.

Clarithromycin and azithromycin have only limited activity against nonsusceptible strains of S. pneumoniae and against β-lactamase–producing strains of nontypeable H. influenzae. Macrolide use also appears to be a major factor in causing increases in rates of resistance to macrolides by group A streptococcus and S. pneumoniae. Clindamycin is active against most strains of S. pneumoniae, including resistant strains, but is not active against nontypeable H. influenzae or M. catarrhalis.

Other antimicrobial agents that have been traditionally utilized in the management of AOM have such significant lack of effectiveness against resistant organisms that employment seldom outweighs the potential side effects or complications possible from the medications. This includes cefprozil, cefaclor, loracarbef, cefixime, trimethoprim-sulfamethoxazole, and erythromycin-sulfisoxazole. Cefpodoxime has demonstrated reasonable effectiveness in some investigations but is generally poorly tolerated because of its taste.

ANTIMICROBIAL PROPHYLAXIS

In children who have developed frequent episodes of AOM, antimicrobial prophylaxis with subtherapeutic doses of an aminopenicillin or a sulphonamide has been utilized in the past to provide protection against recurrences of AOM (although not of OME). However, because of the increased incidence of resistant organisms and the contribution of antimicrobial usage to bacterial resistance, the risks of sustained antimicrobial prophylaxis clearly outweigh potential benefits.

Mycingotomy and Tympanocentesis

Mycingotomy is a long-standing treatment for AOM but is not commonly needed in children receiving antimicrobials. Indications for myringotomy in children with AOM include severe, refractory pain; hyperpyrexia; complications of AOM such as facial paralysis, mastoiditis, labyrinthitis, or central nervous system infection; and immunologic compromise from any source. Myringotomy should be considered as third-line therapy in patients that have failed 2 courses of antibiotics for an episode of AOM. In children with AOM in whom clinical response to vigorous, second-line treatment has been unsatisfactory, either diagnostic tympanocentesis or myringotomy is indicated to enable identification of the offending organism and its sensitivity profile. Either procedure may be helpful in effecting relief of pain. Tympanocentesis with culture of the middle-ear aspirate may also be indicated as part of the sepsis work-up in very young infants with AOM who show systemic signs of illness such as fever, vomiting, or lethargy, and whose illness accordingly cannot be presumed to be limited to infection of the middle ear. Performing tympanocentesis can be facilitated by use of a specially designed tympanocentesis aspirator. Studies reporting the usage of strict, individualized criteria for the diagnosis of AOM that include office tympanocentesis with bacterial culture followed by culture-guided antimicrobial therapy demonstrate significant reduction in the frequency of recurrent AOM episodes and
tympanostomy tube surgery. However, many primary care physicians do not feel comfortable performing this procedure, there is the potential for complications, and parents may view this procedure as traumatic. Often children requiring this intervention have a strong enough history of recurrent OM to warrant the consideration of tympanostomy tube placement, so that the procedure can be performed under general anesthesia.

**Early Recurrence After Treatment**

Recurrence of AOM after apparent resolution may be caused by either incomplete eradication of infection in the middle ear or upper respiratory tract reinfecction by the same or a different bacteria or bacterial strain. Recent antibiotic therapy predisposes patients to an increased incidence of resistant organisms, which should also be considered in choosing therapy, and, generally, initiating therapy with a second-line agent is advisable (see Table 640-3).

**Myringotomy and Insertion of Tympanostomy Tubes**

When AOM is recurrent, despite appropriate medical therapy, consideration of surgical management of AOM with tympanostomy tube insertion is warranted. This procedure is effective in reducing the rate of AOM in patients with recurrent OM and in significantly improving the quality of life in patients with recurrent AOM. Individual patient factors, including the risk profile, severity of AOM episodes, child's development and age, presence of a history of adverse drug reactions, concurrent medical problems, and parental wishes, will affect the timing of a decision to consider referral for this procedure. When a patient experiences 3 episodes of AOM in a 6 mo period or 4 episodes in a 12 mo period with 1 episode in the preceding 6 mo, potential surgical management of the child's AOM should be discussed with the parents. Additionally, often patients with recurrent AOM may have persisting MEE between episodes with accompanying hearing loss, which may add to the indication for tympanostomy tube placement.

**Tube Otorrhea**

Although tympanostomy tubes often reduce the incidence of AOM in most children, patients with tympanostomy tubes may still develop AOM. One advantage of tympanostomy tubes in children with recurrent AOM is that if patients do develop an episode of AOM with a functioning tube in place, these patients will manifest purulent drainage from the tube. By definition, children with functioning tympanostomy tubes without otorrhea do not have bacterial AOM as a cause for a presentation of fever or behavioral changes and should not be treated with oral antibiotics. If tympanostomy tube otorrhea develops, ototopical treatment should be considered as first-line therapy. With a functioning tube in place, the infection is able to drain, there is usually negligible pain associated with the infection, and the possibility of developing a serious complication from an episode of AOM is extremely remote. The current quinolone otic drops approved by the U.S. Food and Drug Administration for use in the middle-ear space in children are formulated with ciprofloxacin/dexamethasone (Ciprodex) and ofloxacin (Floxin). The topical delivery of these otic drops allows them to utilize a higher antibiotic concentration than can be tolerated by administering oral antibiotics and they have excellent coverage of even the most resistant strains of common middle-ear pathogens as well as coverage of *S. aureus* and *Pseudomonas aeruginosa*. The high rate of success of these topical preparations, their broad coverage, the lower likelihood of their contributing to the development of resistant organisms, the relative ease of administration, the lack of significant side effects, and the lack of ototoxicity makes them the first choice for tube otorrhea. Oral antibiotic therapy should generally be reserved for cases of tube otorrhea that have other associated systemic symptoms, patients who have difficulty in tolerating the use of topical preparations, or, possibly, patients who have failed an attempt at topical otic drops. Despite these advantages of ototopical therapy, survey data have indicated that, compared to otolaryngologists, primary care practitioners are less likely to prescribe ototopicals as first-line therapy in tympanostomy tube otorrhea. As a result of the relative ease in obtaining fluid for culture and the possibility of the development of fungal otitis, which has shown an increase with the utilization of broad-spectrum quinolone ototopicals, patients that fail topical therapy should also have culture performed to rule out the development of fungal otitis. Other otic preparations are available; although these either have some risk of ototoxicity or have not received approval for use in the middle ear, many of these preparations were widely used prior to the development of the current quinolone drops and were generally considered reasonably safe and effective. In all cases of tube otorrhea, attention to aural toilet (e.g., cleansing the external auditory canal of secretions, and avoidance of external ear water contamination) is important. In some cases with very thick, tenacious discharge, topical therapy may be inhibited due to lack of delivery of the medication to the site of infection. Suctioning and removal of the secretions, often done through referral to an otolaryngologist, may be quite helpful. When children with tube otorrhea fail to improve satisfactorily with conventional outpatient management, they may require tube removal, or hospitalization to receive parenteral antibiotic treatment, or both.

**MANAGEMENT OF OTITIS MEDIA WITH EFFUSION**

Management of OME depends on an understanding of its natural history and its possible complications and sequelae. Most cases of OME resolve without treatment within 3 mo. To distinguish between persistence and recurrence, examination should be conducted monthly until resolution; hearing should be assessed if effusion has been present for longer than 3 mo. When MEE persists for longer than 3 mo, consideration of referral to an otolaryngologist may be appropriate. For young children, this referral is warranted for the assessment of hearing levels. In older children (generally older than age 4 yr), and depending upon the expertise in the primary care physician's office, hearing screening may be achieved by the primary care physician. For any child who fails a hearing screening in the primary care physician's office, referral to an otolaryngologist is warranted. In considering the decision to refer the patient for consultation, the clinician should attempt to determine the impact of the OME on the child. Although hearing loss may be of primary concern, OME causes a number of other difficulties in children that should also be considered. These include predisposition to recurring AOM, pain, disturbance of balance, and tinnitus. In addition, long-term sequelae that have been demonstrated to be associated with OME include pathologic middle-ear changes; atelectasis of the TM and retraction pocket formation; adhesive OM; cholesteatoma formation and ossicular discontinuity; and conductive and sensorineural hearing loss. Long-term adverse effects on speech, language, cognitive, and psychosocial development have also been demonstrated. This impact is related to the duration of effusion present, whether the effusion is unilateral or bilateral, the degree of underlying hearing loss, and other developmental and social factors affecting the child. In considering the impact of OME on development, it is especially important to take into consideration the overall presentation of the child. Although it is unlikely that OME causing unilateral hearing loss in the mild range will have long-term negative effects on an otherwise healthy and developmentally normal child, even a mild hearing loss in a child with other developmental or speech delays certainly has the potential to compound this child's difficulties (Table 640-4). At a minimum, children with OME persisting longer than 3 mo deserve close monitoring of their hearing levels with skilled audiologic evaluation; frequent assessment of developmental milestones, including speech and language assessment; and attention paid to their rate of recurrent AOM. 

**Variables Influencing Otitis Media with Effusion Management Decisions**

Patient-related variables that affect decisions on how to manage OME include the child's age; the frequency and severity of previous episodes of AOM and the interval since the last episode; the child's current speech and language development; the presence of a history of adverse drug reactions, concurrent medical problems, or risk factors such as daycare attendance; and the parental wishes. In considering surgical management of OME with tympanostomy tubes, particular benefit is
generally 3-6 mo or perhaps longer in children with unilateral effusion, when OME persists despite an ample period of watchful waiting, tympanostomy tubes have variable duration of efficacy based on design. Tubes that are designed for a shorter duration, 6-12 mo, have a lesser impact on disease-free middle-ear spaces in children. Some studies comparing the efficacy of tympanostomy tube types, including shorter-acting tubes, with watchful waiting provide a less helpful assessment of the differences between these approaches. Tubes that are somewhat longer acting, effective for 12-18 mo, are generally more appropriate for most children undergoing tube placement. Regardless of type, tympanostomy tube placement nearly uniformly reverses the conductive hearing loss associated with OME. Occasional episodes of obstruction of the tube lumen and premature tube extrusion may limit the effectiveness of tympanostomy tubes, and tubes can also be associated with otorrhea. However, placement of tympanostomy tubes is generally quite effective in providing resolution of OME in children. Tympanostomy tubes generally extrude on their own but rarely require surgical removal after several years in place. Sequelea following tube extrusion include residual perforation of the eardrum, tympanosclerosis, localized or diffuse atrophic scarring of the eardrum that may predispose to the development of atelectasis or a retraction pocket, or both, residual conductive hearing loss, and cholesteatoma. The more serious of these sequelae are quite infrequent. Recurrence of middle-ear effusion following the extrusion of tubes does develop, especially in younger children; most children without underlying craniofacial abnormalities only require 1 set of tympanostomy tubes, with developmental changes providing improved middle-ear health and resolution of chronic OME by the time of tube extrusion. Because even previously persistent OME often clears spontaneously during the summer mo, watchful waiting through the summer season is also advisable in most children with OME who are otherwise well. In considering surgical management of OME in children, primarily in those with bilateral disease and hearing loss, it has been demonstrated that placement of tympanostomy tubes results in a significant improvement in their quality of life.

Medical Treatment

In some studies, antimicrobials have demonstrated some efficacy in resolving OME, presumably because they help eradicate nasopharyngeal infection or unapparent middle-ear infection, or both. The most significant effects of antibiotics for OME have been shown with treatment durations of 4 wk and 3 mo. However, in the current era of bacterial antimicrobial resistance, the small potential benefit of antimicrobial therapy is outweighed by the negative potential of treatment and is not recommended. Instead, treatment should be limited to cases in which there is evidence of associated bacterial upper respiratory tract infection or untreated middle-ear infection. For this purpose, the most broadly effective drug available should be used as recommended for AOM.

The efficacy of corticosteroids in the treatment of OME is probably short term. The risk: benefit ratio for steroids would argue against their use. Antihistamine-decongestant combinations are not effective in treating children with OME. Antihistamines alone, decongestants alone, and mucolytic agents are unlikely to be effective. The risk profile for decongestants and antihistamines in children suggests that they are not indicated in the treatment of OME. Allergic management, including antihistamine therapy, might prove helpful in children with problematic OME who also have evidence of environmental allergies, although supporting data specifically analyzing this patient population are not conclusive. Recent randomized controlled trials do not support the usage of topical intranasal steroid sprays to treat the manifestations of eustachian tube dysfunction. Inflation of the eustachian tube by the Valsalva maneuver or other means has not demonstrated long-term efficacy but is unlikely to lead to significant harm. Other “alternative” therapies, including spinal manipulation, currently have no demonstrated efficacy or role in children with OME.

Myringotomy and Insertion of Tympanostomy Tubes

When OME persists despite an ample period of watchful waiting, generally 3-6 mo or perhaps longer in children with unilateral effusion, consideration of surgical intervention with tympanostomy tubes is appropriate. Myringotomy alone, without tympanostomy tube insertion, permits evacuation of middle-ear effusion and may sometimes be effective, but often the incision heals before the middle-ear mucosa returns to normal and the effusion soon reaccumulates. Inserting a tympanostomy tube offers the likelihood that middle-ear ventilation will be sustained for at least as long as the tube remains in place and functional. Tympanostomy tubes have a variable duration of efficacy based on design. Tubes that are designed for a shorter duration, 6-12 mo, have a lesser impact on disease-free middle-ear spaces in children. Some studies comparing the efficacy of tympanostomy tube types, including shorter-acting tubes, with watchful waiting provide a less helpful assessment of the differences between these approaches. Tubes that are somewhat longer acting, effective for 12-18 mo, are generally more appropriate for most children undergoing tube placement. Regardless of type, tympanostomy tube placement nearly uniformly reverses the conductive hearing loss associated with OME. Occasional episodes of obstruction of the tube lumen and premature tube extrusion may limit the effectiveness of tympanostomy tubes, and tubes can also be associated with otorrhea. However, placement of tympanostomy tubes is generally quite effective in providing resolution of OME in children. Tympanostomy tubes generally extrude on their own but rarely require surgical removal after several years in place. Sequelea following tube extrusion include residual perforation of the eardrum, tympanosclerosis, localized or diffuse atrophic scarring of the eardrum that may predispose to the development of atelectasis or a retraction pocket, or both, residual conductive hearing loss, and cholesteatoma. The more serious of these sequelae are quite infrequent. Recurrence of middle-ear effusion following the extrusion of tubes does develop, especially in younger children; most children without underlying craniofacial abnormalities only require 1 set of tympanostomy tubes, with developmental changes providing improved middle-ear health and resolution of chronic OME by the time of tube extrusion. Because even previously persistent OME often clears spontaneously during the summer mo, watchful waiting through the summer season is also advisable in most children with OME who are otherwise well. In considering surgical management of OME in children, primarily in those with bilateral disease and hearing loss, it has been demonstrated that placement of tympanostomy tubes results in a significant improvement in their quality of life.

Adenoidectomy

Adenoidectomy is efficacious to some extent in reducing the risk of subsequent recurrences of both AOM and OME in children who have undergone tube insertion and in whom, after extrusion of tubes, OM continues to be a problem. Efficacy appears to be independent of adenoid size and probably derives from removal of the focus of infection in the nasopharynx as a site of biofilm formation, chronic inflammation impacting eustachian tube function, and recurrent seeding of the middle ear via the eustachian tube. In younger children with recurrent AOM who have not previously undergone tube insertion, adenoidectomy is usually not recommended along with tube insertion, unless significant nasal airway obstruction or recurrent rhinosinusitis is associated, in which case, performing adenoidectomy might be considered.

Complications of Acute Otitis Media

Most complications of AOM consist of the spread of infection to adjoining or nearby structures or the development of chronicity, or both. Suppurative complications are relatively uncommon in children in developed countries but occur not infrequently in disadvantaged children whose medical care is limited. The complications of AOM may be classified as either intratemporal or intracranial.

Intratemporal Complications

Direct but limited extension of AOM leads to complications within the local region of the ear and temporal bone. These complications include dermatitis, TM perforation, chronic suppurative OM (CSOM), mastoiditis, hearing loss, facial nerve paralysis, cholesteatoma formation, and labyrinthitis.
Infectious Dermatitis

This is an infection of the skin of the external auditory canal resulting from contamination by purulent discharge from the middle ear. The skin is often erythematous, edematous, and tender. Management consists of proper hygiene combined with systemic antimicrobials and ototopical drops as appropriate for treating AOM and tube otorhea.

Tympanic Membrane Perforation

Rupture of the TM can occur with episodes of either AOM or OME. Although damage to the TM from these episodes generally heals spontaneously, chronic perforations can develop in a small number of cases and require further surgical intervention in the future.

Chronic Suppurative Otitis Media

CSOM consists of persistent middle-ear infection with discharge through a TM perforation. The disease is initiated by an episode of AOM with rupture of the membrane. The mastoid air cells are invariably involved. The most common etiologic organisms are *P. aeruginosa* and *S. aureus*; however, the typical AOM bacterial pathogens may also be the cause, especially in younger children or in the winter months. Treatment is guided by the results of microbiologic investigation. If an associated cholesteatoma is not present, parenteral antimicrobial treatment combined with assiduous aural cleansing is likely to be successful in clearing the infection, but in refractory cases, tympanomastoidectomy can be required.

Acute Mastoiditis

Technically, all cases of AOM are accompanied by mastoiditis by virtue of the associated contiguous inflammation of the mastoid air cells. However, early in the course of the disease, no signs or symptoms of mastoid infection are present, and the inflammatory process usually is readily reversible, along with the AOM, in response to antimicrobial treatment. Spread of the infection to the overlying peristeum, but without involvement of bone, constitutes acute mastoiditis with periosteitis. In such cases, signs of mastoiditis are usually present, including redness and swelling in the postauricular area, often with protrusion and displacement of the pinna inferiorly and anteriorly (Fig. 640-7 and Table 640-5). Treatment with myringotomy and parenteral antibiotics, if instituted promptly, usually provides satisfactory resolution.

In acute mastoid osteitis, or coalescent mastoiditis, infection has progressed further to cause destruction of the bony trabeculae of the mastoid. Frank signs and symptoms of mastoiditis are usually present, but not always, present. In acute petrositis, infection has extended further to involve the petrous portion of the temporal bone. Eye pain, a result of irritation of the ophthalmic branch of cranial nerve V, is a prominent symptom. Cranial nerve VI palsy is a later finding, suggesting further extension of the infectious process along the cranial base. Gradenigo syndrome is the triad of suppurative OM, paralysis of the cranial nerves, and pain in the ipsilateral orbit. Rarely, mastoid infection spreads external to the temporal bone into the neck musculature that attaches to the mastoid tip, resulting in an abscess in the neck, termed a Bezold abscess.

When mastoiditis is suspected or diagnosed clinically, CT scanning of the temporal bones can be considered to further clarify the nature and extent of the disease. Bony destruction of the mastoid must be differentiated from the simple clouding of mastoid air cells that is found often in uncomplicated cases of OM. The most common causative organisms in all variants of acute mastoiditis are *S. pneumoniae*, group A streptococcus, and nontypeable *H. influenzae*. *P. aeruginosa* is also a causative agent, primarily in patients with CSOM. Children with acute mastoid osteitis generally require intravenous antimicrobial treatment and mastoidectomy, with the extent of the surgery dependent on the extent of the disease process. Early cases of mastoid osteitis may respond to myringotomy and parenteral antibiotics. Insomuch as possible, choice of the antimicrobial regimen should be guided by the findings of microbiologic examination from cultures.

Each of the variants of mastoiditis may also occur in subacute or chronic form. Symptoms are correspondingly less prominent. Chronic mastoiditis is always accompanied by CSOM, and occasionally will respond to the conservative regimen recommended for that condition. In most cases, mastoidectomy also is required.

Facial Paralysis

The facial nerve, as it traverses the middle ear and mastoid bone, may be affected by adjacent infection. Facial paralysis occurring as a complication of AOM is uncommon, and often resolves after myringotomy and parenteral antibiotic treatment. Facial paralysis in the presence of AOM requires urgent attention as prolonged infection can result in the development of permanent facial paralysis, which can have a devastating effect on a child. Facial paralysis in an infant or child requires complete and unequivocal examination of the TM and middle-ear...
Life-threatening consequences. Acquired cholesteatoma commonly involves the mastoid cavity, and may extend intracranially with potentially extensive bony resorption, often extending into the tympanic membrane (TM) or insertion of a tympanostomy tube. Cholesteatomas tend to develop as a deep retraction pocket of the TM or as a consequence of epithelial implantation in the middle-ear cavity from traumatic perforation of the TM or insertion of a tympanostomy tube. Cholesteatomas tend to expand progressively, causing bony resorption, often extend into the mastoid cavity, and may extend intracranially with potentially life-threatening consequences. Acquired cholesteatoma commonly presents as a chronically draining ear in a patient with a history of previous ear disease. Cholesteatoma should be suspected if otoscopy demonstrates an area of TM retraction or perforation with white, caseous debris persistently overlying this area. Along with otorrhea from this area, granulation tissue or polyp formation identified in conjunction with this history and presentation should prompt suspicion of cholesteatoma. The most common location for cholesteatoma development is in the superior portion of the TM (pars flaccida). Most patients also present with conductive hearing loss on audiologic evaluation. When cholesteatoma is suspected, otolaryngology consultation should be sought immediately. Delay in recognition and treatment can have significant long-term consequences, including the need for more extensive surgical treatment, permanent hearing loss, facial nerve injury, labyrinthine damage with loss of balance function, and intracranial extension. The required treatment for cholesteatoma is tympanomastoid surgery.

Congenital cholesteatoma is an uncommon condition generally identified in younger patients (Fig. 640-9). The etiology of congenital cholesteatoma is thought to be a result of epithelial implantation in the middle-ear space during otologic development in utero. Congenital cholesteatoma most commonly presents in the anterior-superior quadrant of the TM but can be found elsewhere. Congenital cholesteatoma appears as a discrete, white opacity in the middle-ear space on otoscopy. Unlike patients with acquired cholesteatoma, there is generally not a strong history of OM or chronic ear disease, history of otorrhea, or changes in the TM anatomy such as perforation or retraction. Similar to acquired cholesteatoma many patients do have some degree of abnormal findings on audiologic evaluation, unless identified very early. Congenital cholesteatoma also requires surgical resection.

Labyrinthitis
This occurs uncommonly as a result of the spread of infection from the middle ear and/or mastoid to the inner ear (see Chapter 641). Cholesteatoma or CSOM is the usual source. Symptoms and signs include vertigo, tinnitus, nausea, vomiting, hearing loss, nystagmus, and clumsiness. Treatment is directed at the underlying condition and must be undertaken promptly to preserve inner-ear function and prevent the spread of infection.

**INTRACRANIAL COMPlications**
Meningitis, epidural abscess, subdural abscess, focal encephalitis, brain abscess (see Chapters 603 and 604), sigmoid sinus thrombosis (also called lateral sinus thrombosis), and otitic hydrocephalus each may develop as a complication of acute or chronic middle-ear or mastoid infection, through direct extension, hematogenous spread, or thrombophlebitis. Bony destruction adjacent to the dura is often involved, and a cholesteatoma may be present. In a child with middle-ear or mastoid infection, the presence of any systemic symptom, such as high fever and meningism, should prompt a rapid search for intracranial extension.

**Table 640-5** Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periosteitis/Abscess

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CREASE*</th>
<th>ERYTHEMA</th>
<th>MASS</th>
<th>TENDERNESS</th>
<th>EXTERNAL CANAL INFECTION</th>
<th>MIDDLE-EAR EFFUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mastoiditis with periosteitis</td>
<td>May be absent</td>
<td>Yes</td>
<td>No</td>
<td>Usually</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Acute mastoiditis with subperiosteal abscess</td>
<td>Absent</td>
<td>Maybe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Periosteitis of pinna with postauricular extension</td>
<td>Intact</td>
<td>Yes</td>
<td>No</td>
<td>Usually</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>External otitis with postauricular extension</td>
<td>Intact</td>
<td>Yes</td>
<td>No</td>
<td>Usually</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Postauricular lymphadenitis</td>
<td>Intact</td>
<td>No</td>
<td>Yes (circumscribed)</td>
<td>Maybe</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Postauricular crease (fold) between pinna and postauricular area.

**Figure 640-8** A retraction pocket cholesteatoma of the posterosuperior quadrant. The incus long process is eroded, which leaves the drum adherent to the stapes head (S). An effusion is present in the middle ear, and squamous debris emanates from the attic. (From Isaccson G: Diagnosis of pediatric cholesteatoma, Pediatrics 120:603–608, 2007, Fig. 9, p. 607.)

**Cholesteatoma**
Cholesteatoma is a cyst-like growth originating in the middle ear, lined by keratinized, stratified squamous epithelium and containing desquamated epithelium and/or keratin (see Chapter 638; Fig. 640-8).

**Acquired cholesteatoma** develops most often as a complication of long-standing chronic OM. The condition also may develop from a deep retraction pocket of the TM or as a consequence of epithelial implantation in the middle-ear cavity from traumatic perforation of the TM or insertion of a tympanostomy tube. Cholesteatomas tend to expand progressively, causing bony resorption, often extend into the mastoid cavity, and may extend intracranially with potentially life-threatening consequences. Acquired cholesteatoma commonly develops most often as a complication of chronic OM or from tympanosinus disease. Acquired cholesteatoma may also present as a Grade 2 or 3 tympanosinus disease, particularly in cases of tympanosinus empyema, where the tympanic membrane retracts into the middle ear.

**Postauricular Signs and Symptoms**

- **EXTERNAL CANAL**
  - Erosion of the TM: present
  - Erosion of the TM: absent
  - Erosion of the TM: maybe
  - Erosion of the TM: no
  - Erosion of the TM: yes

- **MIDDLE-EAR EFFUSION**
  - Erosion of the TM: present
  - Erosion of the TM: absent
  - Erosion of the TM: maybe
  - Erosion of the TM: no
  - Erosion of the TM: yes

**Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periosteitis/Abscess**

**Ear Infections**

- **Acute mastoiditis** with periosteitis
  - Absent
  - Present

- **Periosteitis of pinna** with postauricular extension
  - Absent
  - Present

- **External otitis** with postauricular extension
  - Absent
  - Present

- **Postauricular lymphadenitis**
  - Absent
  - Present

**Head Infections**

- **Meningitis**
  - Absent
  - Present

- **Epidural abscess**
  - Absent
  - Present

- **Subdural abscess**
  - Absent
  - Present

- **Bacterial vertebral osteomyelitis**
  - Absent
  - Present

- **Bone and joint infections**
  - Absent
  - Present

- **Fungal osteomycosis**
  - Absent
  - Present

- **Dermatologic infections**
  - Absent
  - Present

**Lymphadenitis**

- **Acute suppurative lymphadenitis**
  - Absent
  - Present

- **Subcutaneous lymphadenitis**
  - Absent
  - Present

**Postauricular Signs and Symptoms**

<table>
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<tr>
<th>Postauricular Signs and Symptoms</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Erosion of the TM</td>
<td>Present</td>
<td>Yes</td>
<td>No</td>
<td>Usually</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Erosion of the TM</td>
<td>Absent</td>
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*Postauricular crease (fold) between pinna and postauricular area.
spiking fevers, headache, or lethargy of extreme degree, or a finding of meningeal rigidity or of any central nervous system sign on physical examination should prompt suspicion of an intracranial complication.

When an intracranial complication is suspected, lumbar puncture should be performed only after imaging studies establish that there is no evidence of mass effect or hydrocephalus. In addition to examination of the cerebrospinal fluid, culture of middle-ear exudate obtained via tympanocentesis may identify the causative organism, thereby helping guide the choice of antimicrobial medications. Myringotomy should be performed to permit middle-ear drainage. Concurrent tympanostomy tube placement is preferable to allow for continued decompression of the “infection under pressure” that is the causative event leading to intracranial spread of the infection.

Treatment of intracranial complications of OM requires urgent, otolaryngologic, and, often, neurosurgical consultation, intravenous antibiotic therapy, drainage of any abscess formation, and tympanomastoidectomy in patients with coalescent mastoiditis.

Sigmoid sinus thrombosis may be complicated by dissemination of infected thrombi with resultant development of septic infarcts in various organs. With prompt recognition and wide availability of MRI, which facilitates diagnosis, this complication is exceedingly rare. Mastoidectomy may be required even in the absence of osteitis or coalescent mastoiditis, especially in the case of propagation or embolization of infected thrombi. In the absence of coalescent mastoiditis, sinus thrombosis can often be treated with tympanostomy tube placement and intravenous antibiotics. Anticoagulation therapy may also be considered in the treatment of sigmoid sinus thrombosis; however, otolaryngology consultation should be obtained before initiating this therapy to coordinate the possible need for surgical intervention prior to anticoagulation.

**Ototic hydrocephalus**, a form of *pseudotumor cerebri* (see Chapter 605), is an uncommon condition that consists of increased intracranial pressure without dilation of the cerebral ventricles, occurring in association with acute or chronic OM or mastoiditis. The condition is commonly also associated with lateral sinus thrombosis, and the pathophysiology is thought to involve obstruction by thrombus of intracranial venous drainage into the neck, producing a rise in cerebral venous pressure and a consequent increase in cerebrospinal fluid pressure. Symptoms are those of increased intracranial pressure. Signs may include, in addition to evidence of OM, paralysis of 1 or both lateral rectus muscles and papilledema with or without visual acuity loss. MRI can confirm the diagnosis. Treatment measures include the use of antimicrobials and medications such as acetazolamide or furosemide to reduce intracranial pressure, mastoidectomy, repeated lumbar puncture, lumbo-peritoneal shunt, and ventriculoperitoneal shunt. If left untreated, otitic hydrocephalus may result in loss of vision secondary to optic atrophy.

### PHYSICAL SEQUELAE

The physical sequelae of OM consist of structural middle-ear abnormalities resulting from long-standing middle-ear inflammation. In most instances, these sequelae are consequences of severe and/or chronic infection, but some may also result from the noninfective inflammation of long-standing OME. The various sequelae may occur singly, or interrelatedly in various combinations.

**Tympanosclerosis** consists of whitish plaques in the TM and nodular deposits in the submucosal layers of the middle ear. The changes involve hyalinization with deposition of calcium and phosphate crystals. Uncommonly, there may be associated conductive hearing loss. In developed countries, probably the most common cause of tympanosclerosis is tympanostomy tube insertion. **Atelectasis** of the TM is a descriptive term applied to either severe retraction of the TM caused by high negative middle-ear pressure or loss of stiffness and medial prolapse of the membrane as a consequence of long-standing retraction or severe or chronic inflammation. A **retraction pocket** is a localized area of atelectasis. Atelectasis is often transient and usually unaccompanied by symptoms, but a deep retraction pocket may lead to erosion of the ossicles and adhesive otitis, and may serve as the nidus of a cholesteatoma. For a deep retraction pocket, and for the unusual instance in which atelectasis is accompanied by symptoms such as otalgia, tinnitus, or conductive hearing loss, the required treatment is tympanostomy tube insertion and, at times, tympanoplasty. Patients with persisting atelectasis and retraction pockets should have referral to an otolaryngologist.

**Adhesive OM** consists of proliferation of fibrous tissue in the middle-ear mucosa, which may, in turn, result in severe TM retraction, conductive hearing loss, impaired movement of the ossicles, ossicular discontinuity, and cholesteatoma. The hearing loss may be amenable to surgical correction.

**Cholesterol granuloma** is an uncommon condition in which the TM may appear to be dark blue secondary to middle-ear fluid of this color. Cholesterol granulomas are rare, benign cysts that occur in the temporal bone. They are expanding masses that contain fluids, lipids, and cholesterol crystals surrounded by a fibrous lining and generally require surgical removal. Tympanostomy tube placement will not provide satisfactory relief. This lesion requires differentiation from bluish middle-ear fluid, which can also rarely develop in patients with the more common OME.

**Chronic perforation** may rarely develop after spontaneous rupture of the TM during an episode of AOM or from acute trauma, but more commonly results as a sequel of CSOM or as a result of failure of closure of the TM following extrusion of a tympanostomy tube. Chronic perforations are generally accompanied by conductive hearing loss. Surgical repair of a TM perforation is recommended to restore hearing, prevent infection from water contamination in the middle-ear space, and prevent cholesteatoma formation. Chronic perforations are almost always amenable to surgical repair, usually after the child has been free of OM for an extended period.

Permanent **conductive hearing loss** (see Chapter 637) may result from any of the conditions just described. Rarely, permanent sensorineural hearing loss may occur in association with acute or chronic OM, secondary to spread of infection or products of inflammation through the round window membrane, or as a consequence of suppurative labyrinthitis.
POSSIBLE DEVELOPMENTAL SEQUELAE
Permanent hearing loss in children has a significant negative impact on development, particularly in speech and language. The degree to which OM impacts long-term development in children is difficult to assess and there have been conflicting studies examining this question. Developmental impact is most likely to be significant in children that have greater levels of hearing loss, hearing loss that is sustained for longer periods of time, or hearing loss that is bilateral and in those children that have other developmental difficulties or risk factors for developmental delay (see Table 640-4).

Bibliography is available at Expert Consult.


Genetic factors can impact the anatomy and function of the inner ear. Infectious agents, including viruses, bacteria, and protozoa, also can cause abnormal function, most commonly as sequelae of congenital infection or bacterial meningitis. Other acquired diseases of the labyrinthise capsule include otosclerosis, osteopetrosis, Langerhans cell histiocytosis, fibrous dysplasia, and other types of bony dysplasia. All of these can cause both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL) as well as vestibular dysfunction. Use of currently available vaccines reduces the risk for bacterial meningitis and the associated sensorineural hearing loss.

**VIRUSES**

The most common cause of childhood sensorineural hearing loss (SNHL) is congenital cytomegalovirus (CMV) infection (see Chapter 255). Although the pathogenesis of hearing loss has not been elucidated, there is histologic evidence of infection in the cells of both the cochlear and vestibular endolabyrinth. The strongest predictor of delayed hearing loss appears to be the presence of symptoms at birth; prolonged viral shedding may also be a risk factor. In one large study, children who passed initial audiologic examinations but who had CMV-related symptoms at birth were approximately 6 times more likely to develop hearing loss than those who were asymptomatic. Stabilization (or even reversal) of the hearing loss may be possible by using ganciclovir in very young infants with congenital CMV infection. Administering ganciclovir for 6 wk improved hearing outcomes in neonates with symptomatic congenital CMV infections involving the central nervous system.

Other viral causes of SNHL include congenital rubella as well as acquired mumps (see Chapter 248), rubella (see Chapter 247), rubella (measles; see Chapter 246), and fifth disease, caused by parvovirus B19 (see Chapter 251). Many other viruses also occasionally are associated with SNHL. In as many as 50% of cases, hearing loss, which usually is bilateral and often is asymmetric, progresses and worsens over weeks to years.

Before an effective vaccine was introduced, rubella was responsible for as many as 60% of cases of childhood SNHL. Vaccination in developed countries has reduced the rate of rubella by >97%. Similarly, measles and mumps are now uncommon causes of SNHL in the United States because of successful vaccination programs.

Herpes simplex encephalitis can also be associated with SNHL, which is more common in children with congenital herpesvirus infection. Acyclovir and other antiviral agents can help the hearing loss and other central nervous system manifestations (see Chapter 245).

**TOXOPLASMOsis**

See Chapter 290.

Toxoplasma gondii is a protozoan that can cause congenital SNHL. In an estimated 1-10 per 10,000 live births in the United States, 1 per 3,000 live births in France, and 1 per 770 live births in southeast Brazil, infants are born each year with congenital toxoplasmosis; approximately 25% of untreated patients have SNHL. If maternal infection is documented during the fetal period, medical therapy may be able to prevent some of the clinical manifestations, including SNHL of the offspring.

**BACTERIAL MENINGITIS**

Since the Haemophilus influenzae type b vaccine was introduced, Streptococcus pneumoniae (see Chapter 182) and Neisseria meningitidis (see Chapter 191) have become the leading causes of bacterial meningitis in children in the United States. Hearing loss occurs more commonly with S. pneumoniae, with an estimated incidence of 15-20%. Approximately 60% of the associated hearing loss is bilateral, although it often is asymmetric. If hearing loss is present at the time of presentation with meningitis, and especially if it is severe to profound, the likelihood of significant improvement is low. However, if the hearing loss develops after admission for treatment and is not severe, stabilization or improvement is possible. Late progression of SNHL also has been noted in some children years after meningitis. In the United States and many other developed countries, bacterial meningitis is one of the major causes of profound deafness leading to cochlear implantation in children. Gadolinium-enhanced MRI could be utilized to detect meningitic labyrinthitis and therefore to predict which patients are at high risk for postmeningitic hearing loss. Gadolinium-enhanced MRI was found to be 87% sensitive and 100% specific for predicting which ears would develop permanent SNHL. The introduction of pneumococcal conjugate vaccine is expected to lead to a reduction in SNHL caused by pneumococcal meningitis, although pneumococcal strains not sensitive to the vaccine appear to be associated with rates of deafness equivalent to those that are sensitive.

Studies have shown favorable trends in the course and outcome after administration of dexamethasone for hearing loss and other neurologic deficits associated with bacterial meningitis (see Chapter 603.1), although its effectiveness, especially for S. pneumoniae and N. meningitidis meningitis, generally has not reached statistical significance because of the small number of cases in the trials. A meta-analysis of 2,029 patients from randomized, double-blinded, placebo-controlled trials of dexamethasone for bacterial meningitis found that adjunctive dexamethasone does not seem to significantly reduce death or neurologic disability but does reduce hearing loss among survivors. Dexamethasone has been shown to reduce severe hearing loss associated with H. influenzae type b meningitis regardless of the timing of administration of dexamethasone (before or with antibiotics vs later) or of the antibiotic used. For pneumococcal meningitis, dexamethasone might confer benefit only when given early and only for protection against severe hearing loss.

**SYPHILIS**

See Chapter 218.

Congenital syphilis, caused by Treponema pallidum, causes SNHL in 3-38% of affected children. The exact incidence is difficult to ascertain, because the hearing loss might not develop until adolescence or even adulthood. When the condition is identified, treatment with antibiotics and corticosteroids can improve the hearing loss.

**OTHER DISEASES OF THE INNER EAR**

Labyrinthitis (also called vestibular neuritis) may be a complication of direct spread of infection from acute or chronic otitis media or mastoiditis and also can complicate bacterial meningitis as a result of organisms entering the labyrinth through the internal auditory meatus, endolymphatic duct, perilymphatic duct, vascular channels, or
hematogenous spread. Clinical manifestations of vestibular neuritis can include a sudden onset of rotatory vertigo, dysequilibrium, postural imbalance (furniture walking) with falls to the affected side, deep-seated ear pain, nausea, vomiting, and spontaneous horizontal (occasionally rotary) nystagmus.

The dizziness may last a few days, but balance issues, particularly following rapid head movements toward the affected ear, may last for more. Vestibular neuritis is usually unilateral and is not associated with other neurologic defects; subjective hearing loss is unusual in vestibular neuritis. If hearing loss is present, idiopathic SNHL should be considered, as well as classical labyrinthitis (vestibular and cochlear nerves). Treatment of vestibular neuritis may include prednisone and vestibular rehabilitative exercises. Recurrent episodes should suggest another diagnosis such as vestibular migraine or benign paroxysmal positional vertigo.

In children, viral labyrinthitis is often associated with hearing loss. Acute suppurative labyrinthitis, characterized by abrupt, severe onset of these symptoms, requires intensive antimicrobial therapy. Vestibular suppressants (dimehydrinate 1-2 mg/kg) can also be used in the acute stage but should not be given for more than 3 days. If it is secondary to otitis media, otologic surgery may be required to remove underlying cholesteatoma or drain the middle ear and mastoid, in addition to antibiotics. Acute serous labyrinthitis, with milder symptoms of vertigo and hearing loss, can develop secondary to middle-ear infection as well. It usually responds well to antibiotics and corticosteroids, with improvement in both vertigo and hearing. Chronic labyrinthitis, most commonly associated with cholesteatoma, manifests with SNHL and vestibular dysfunction that develops over time; surgery is required to remove the cholesteatoma. Chronic labyrinthitis also occurs uncommonly secondary to long-standing otitis media, with the slow development of SNHL, usually starting in the higher frequencies, and possibly with vestibular dysfunction. Additionally, and more commonly, children with chronic middle-ear fluid often are unsteady or off balance, a situation that improves immediately when the fluid resolves.

Vertigo and dizziness are common among older children and adolescents. Benign paroxysmal vertigo is common and is characterized by short periods of vertigo or dizziness lasting seconds to a few min and is associated with imbalance and nystagmus; tinnitus or hearing loss is unusual. Basilar/vestibular migraine is a common cause of episodic vertigo or dizziness and is associated with headache (50-70% of patients), rotary or to and fro nystagmus, and sensitivity to noise and bright light (see Chapter 595.1). Benign paroxysmal positional vertigo is less common in young children and more common with increasing age into adulthood. Particles form in the semicircular canals (canalolithiasis), most often the posterior canal; symptoms occur with position changes of the head and may last sec to min. Vertigo and nystagmus may be demonstrated by changing position (sitting to lying down on the right or left). Treatment involves canalith repositioning maneuvers to shift the debris from the canals into the utricle.

Otosclerosis, an autosomal dominant disease that affects only the temporal bones, causes abnormal bone growth that can result in fixation of the stapes in the oval window, leading to progressive hearing loss. In one series in North America, otosclerosis was found in 0.6% of temporal bones of children younger than 5 yr of age and 4% of those ages 5-18 yr. The hearing loss is usually conductive at first, but SNHL can develop. White girls and women are affected most commonly, with onset of otosclerosis in teenagers or young adults, often associated with pregnancy. Corrective surgery to replace the stapes with a mobile prosthesis often is successful.

Osteogenesis imperfecta is a systemic disease that can involve both the middle and inner ears (see Chapter 701). Hearing loss occurs in approximately 20% of young children and as many as 90% of adults with this disease. The hearing loss most commonly is conductive because of abnormalities of the ossicles, but SNHL can occur if other areas of the otic capsule become affected. Hearing loss may be the result of clinical or cochlear otosclerosis, fracture or atrophy of the ossicles, and/or cochlear degeneration due to an unidentified mechanism. An association between bone mineral density and hearing loss in osteogenesis imperfecta has been demonstrated, suggesting that patients with lower bone mineral density are more susceptible to microfractures, which may lead to the conductive hearing loss component. If the hearing loss is severe enough, a hearing aid may be a preferable alternative to surgical correction of the fixed stapes, because stapedectomy in children with osteogenesis imperfecta can be technically very difficult, and the disease and the hearing loss may be progressive.

Osteopetrosis, a very uncommon skeletal dysplasia, can involve the temporal bone, including the middle ear and ossicles, resulting in a moderate to severe, usually conductive hearing loss. Recurrent facial nerve paralysis also can occur as a result of excess bone deposition; with each recurrence, less facial function might return (see Chapter 699).

Bibliography is available at Expert Consult.
Bibliography


AURICLE AND EXTERNAL AUDITORY CANAL

Auricle trauma is common in certain sports. Hematoma, with accumulation of blood between the perichondrium and the cartilage, can follow trauma to the pinna and is especially common in teenagers related to wrestling or boxing. Prompt drainage of a hematoma can prevent irreversible damage. Immediate needle aspiration or, when the hematoma is extensive or recurrent, incision and drainage and a pressure dressing are necessary to prevent perichondritis, which can result in cartilage loss and a "cauliflower ear deformity." Sports helmets should be worn when appropriate during activities when head trauma is possible.

Frostbite of the auricle should be managed by rapidly rewarming the exposed pinna with warm irrigation or warm compresses.

Foreign bodies in the external canal are common in childhood. Often these can be removed in the office setting without general anesthesia if the child is mature enough to understand and cooperate and is properly restrained; if an adequate headlight, surgical head otoscope, or otomicroscope is used for visualizing the object; and if appropriate instruments such as alligator forceps, wire loops or a blunt cerumen curette, or suction are used, depending on the shape of the object. Gentle irrigation of the ear canal with body temperature water or saline may be used to remove very small objects, but only if the tympanic membrane (TM) is intact. Attempts to remove an object from a struggling child or with poor visualization and inadequate tools result in a terrified child with a swollen and bleeding ear canal and can then mandate general anesthesia to remove the object. Difficult foreign bodies, especially those that are large, deeply embedded, or associated with canal swelling, are best removed by an otolaryngologist and/or under general anesthesia. Disk batteries are removed emergently because they leach a basic fluid that can cause severe tissue destruction. Insects in the canal are first killed with mineral oil or lidocaine and are then removed under otomicroscopic examination.

After a foreign body is removed from the external canal, the TM should be inspected carefully for possible traumatic perforation or for a preexisting middle-ear effusion. If a foreign body has resulted in acute inflammation of the canal, ear drop treatment as described for acute external otitis should be instituted (see Chapter 639).
TEMPORAL BONE FRACTURES

Children are particularly prone to basilar skull fractures, which usually involve the temporal bone. Temporal bone trauma should be considered in head injuries, and the status of the ear and hearing should be evaluated. Temporal bone fractures are divided into longitudinal (70-80%), transverse, and mixed. Longitudinal fractures (Fig. 642-2) are commonly manifested by bleeding from a laceration of the external canal or TM; postauricular ecchymosis (Battle sign); hemotympanum (blood behind an intact TM); conductive hearing loss resulting from TM perforation, hemotympanum, or ossicular injury; delayed onset of facial paralysis (which usually improves spontaneously); and temporary CSF otorrhea or rhinorrhea (from CSF running down the eustachian tube). Transverse fractures of the temporal bone have a graver prognosis than longitudinal fractures and are often associated with immediate facial paralysis. Facial paralysis might improve if caused by edema, but surgical decompression of the nerve is often recommended if there is no evidence of clinical recovery and facial nerve studies are unfavorable. If the facial nerve has been transected, surgical decompression and anastomosis offer the possibility of some functional recovery. Transverse fractures are also associated with severe SNHL, vertigo, nystagmus, tinnitus, nausea, and vomiting associated with loss of cochlear and vestibular function; hemotympanum; rarely, external canal bleeding; and CSF otorrhea, either in the external auditory canal or behind the TM, which can exit the nose via the eustachian tube. If temporal bone fracture is suspected or seen on radiographs, gentle examination of the pinna and ear canal is indicated; lacerations or behind the TM, which can exit the nose via the eustachian tube.

If temporal bone fracture is suspected or seen on radiographs, gentle examination of the pinna and ear canal is indicated; lacerations or avulsion of soft tissue is common with temporal bone fractures. Vigorous removal of external auditory canal blood clots or tympanocentesis is not indicated, because removing the clot can further dislodge the ossicles or reopen CSF leaks. The effectiveness of prophylactic antibiotics to prevent meningitis in patients with basilar skull fractures and CSF otorrhea or rhinorrhea cannot be determined because studies to date are flawed by biases. If a patient is febrile and the drainage is not cloudy, watchful waiting without antibiotics is indicated. Surgical intervention is reserved for children who require repair of a nonhealing TM perforation, who have suffered dislocation of the ossicular chain, or who need decompression of the facial nerve. SNHL can also follow a blow to the head without an obvious fracture of the temporal bone (labyrintheal concussion).

ACOUSTIC TRAUMA

Acoustic trauma results from exposure to high-intensity sound (fireworks, gunfire, loud music, heavy machinery) and is initially
manifested by a temporary decrease in the hearing threshold, most commonly at 4,000 Hz on an audiometric examination, and tinnitus. If the sound is between 85 and 140 dB, the loss is usually temporary (after a rock concert), but both the hearing loss and the tinnitus can become permanent with chronic noise exposure; the frequencies from 3,000-6,000 Hz are most often involved. Sudden, extremely loud (>140 dB), short-duration noises with loud peak components (gunfire, bombs) can cause permanent hearing loss after a single exposure. Noise-induced hearing loss results from interactions between genes and the environment. Ear protection and avoidance of chronic exposure to loud noise are preventive measures. Hearing loss from chronic noise exposure should be entirely preventable. Parents should be made aware of the dangers of acoustic trauma, from the environment and from the use of headphones, and should take measures to minimize exposure. Treatment with high-dose steroids for 1-2 wk should be considered to treat acute hearing loss related to noise trauma.

Bibliography is available at Expert Consult.
Bibliography
Benign tumors of the external canal include osteomas and monostotic and polyostotic fibrous dysplasia. Osteomas manifest as bony masses in the canal and require removal only if hearing is impaired or external otitis results; osteomas may be confused clinically with exostoses (see Chapter 501.2). Masses occurring over the mastoid bone, such as first branchial cysts, dermoid cysts, and lipomas, may be confused with primary mastoid tumors; imaging can help with the diagnosis and treatment plan.

Eosinophilic granuloma, which can occur in isolation or as part of the systemic Langerhans cell histiocytosis (see Chapter 507), should be suspected in patients with otalgia, otorrhea (sometimes bloody), hearing loss, abnormal tissue within the middle ear or ear canal, and roentgenographic findings of a sharply delineated destructive lesion of the temporal bone. Definitive diagnosis is made by biopsy. Treatment depends on the site of the lesion and histology. Depending on the site, it may be treated by surgical excision, curettage, or local radiation. If the lesion is part of a systemic presentation of Langerhans cell histiocytosis, chemotherapy in addition to local therapy (surgery with or without radiation) is indicated. Long-term follow-up is necessary whether the temporal bone lesion is a single isolated lesion or part of a multisystem disease.

Symptoms and signs of rhabdomyosarcoma (see Chapter 500) originating in the middle ear or ear canal include a mass or polyp in the middle ear or ear canal, bleeding from the ear, otorrhea, otalgia, facial paralysis, and hearing loss. Other cranial nerves also may be involved. Diagnosis is based on biopsy, but the extent of disease is determined by both CT and MRI of the temporal and facial bones, skull base, and brain (Fig. 643-1). Management usually involves a combination of chemotherapy, radiation, and surgery.

Non-Hodgkin lymphoma (see Chapter 496.2) and leukemia (see Chapter 495) also occur rarely in the temporal bone. Although primary neoplasms of the middle ear are very uncommon in children, they include adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma. Benign tumors of the temporal bone include glomus tumors. The initial signs and symptoms of the more common nasopharyngeal neoplasms (angiofibroma, rhabdomyosarcoma, epidermoid carcinoma) may be associated with insidious onset of chronic otitis media with effusion (often unilateral). A high index of suspicion is needed for diagnosing these tumors early.

Bibliography is available at Expert Consult.
Bibliography
Morphology of the Skin
Brianne Z. Dickey and Yvonne E. Chiu

EPIDERMIS
The mature epidermis is a stratified epithelial tissue composed predominantly of keratinocytes. The function of the epidermis is protection of the organism from the external environment, through physical, chemical, and immunologic barrier functions, and the prevention of water loss. The process of epidermal differentiation results in the formation of a functional barrier to the external world. The epidermis comprises four histologically recognizable layers, described here from deepest to most superficial. The first or basal layer consists of columnar cells that rest on the dermal–epidermal junction. Basal keratinocytes are connected to the dermal–epidermal junction by hemidesmosomes. Basal keratinocytes are attached to themselves and to the cells in the spinous layer by desmosomal, tight, gap, and adherens junctions. The role of the basal keratinocyte is to serve as a continuing supply of keratinocytes for the normally differentiating epidermis as well as a reservoir of cells to repair epidermal damage. The second layer is the spinous layer, composed of 3-4 layers of spinous cells. Their role is to synthesize keratin, which makes up the keratin intermediate filament network. The third layer is the granular layer, which consists of 2-3 layers of granular cells. Granular cells contain keratohyalin and lamellar granules, containing the protein and lipid components that make up the cornified layer. The fourth layer, or cornified layer, is composed of multiple layers of dead, highly compacted cells. The dead cells are composed mainly of desulfide-bonded keratin filaments crosslinked by filaggrins. The intercellular spaces are composed of hydrophobic lipids, predominantly ceramides, cholesterol, and fatty acids, serving as an effective barrier against water and salt loss as well as permeation of water-soluble substances. As the cornified layer is replenished, the oldest or most superficial layer is shed in a highly regulated process. The normal process of epidermal differentiation from basal cell to shedding of cornified layer takes 28 days.

The epidermis also contains 3 other cell types. The melanocytes are pigment-forming cells, which are responsible for skin color and protection from ultraviolet radiation. Epidermal melanocytes are derived from the neural crest and migrate to the skin during embryonic life. They reside in the interfollicular epidermis and in the hair follicles. Melanocytes produce intracellular organelles (melanosomes) containing melanin, which they transfer via dendrites to the keratinocytes to protect the keratinocyte nucleus from ultraviolet damage. Merkel cells are type I slow-adapting mechanosensory receptors for touch that differentiate within the epidermis from epidermal progenitor cells. Langerhans cells are dendritic cells of the mononuclear phagocyte system. They are recognized electron microscopically by a specific organelle, the Birbeck granule. These cells are derived from bone marrow and participate in immune reactions in the skin, playing an active part in antigen presentation and processing.

The function of the epidermis and dermis is the basement membrane zone. This complex structure is a result of contributions from both epidermal and mesenchymal cells. The dermal-epidermal junction extends from the basal cell plasma membrane to the uppermost region of the dermis. Ultrastructurally, the basement membrane appears as a trilaminar structure, consisting of a lamina lucida immediately adjacent to the basal cell plasma membrane, a central lamina densa, and the subbasal lamina on the dermal side of the lamina densa. Several structures within this zone act to anchor the epidermis to the dermis. The plasma membrane of basal cells contains electron-dense plates known as hemidesmosomes; tonofilaments course within basal cells to insert at these sites. The hemidesmosomes are composed of 180- and 230-kDa bullous pemphigoid antigens (BP180 [type XVII collagen] and BP230, respectively), α6β4 and α7β1 integrins, and plectin. Anchoring filaments originate in the plasma membrane, primarily near the hemidesmosomes, and insert into the lamina densa. Anchoring fibrils, composed predominantly of type VII collagen, extend from the lamina densa into the uppermost dermis, where they loop through collagen fibrils before reinserting into the lamina densa.

DERMIS
The dermis provides the skin with most of its mechanical properties. The dermis forms a tough, pliable, fibrous supporting structure between the epidermis and the subcutaneous fat. The predominant dermal cell is a spindle-shaped fibroblast that is responsible for the synthesis of collagen, elastic fibers, and mucopolysaccharides. Phagocytic histiocytes, mast cells, and motile leukocytes are also present. Within the dermis are blood vessels, lymphatics, neural structures, eccrine and apocrine sweat glands, hair follicles, sebaceous glands, and smooth muscle. Morphologically, the dermis can be divided into 2 layers: the superficial papillary layer that interdigitates with the rete ridges of the epidermis and the deeper reticular layer that lies beneath the papillary dermis. The papillary layer is less dense and more cellular, whereas the reticular layer appears more compact because of the coarse network of interlaced collagen and elastic fibers.

The extracellular matrix of the dermis consists of collagen and elastic fibers embedded in an amorphous ground substance. Collagen provides strength and stability to the dermis, while elastic fibers allow for elasticity. The gelatinous ground substance serves as a supporting medium for the fibrillar and cellular components and as a storage place for a substantial portion of body water.

SUBCUTANEOUS TISSUE
The panniculus, or subcutaneous tissue, consists of fat cells and fibrous septa that divide it into lobules and anchor it to the underlying fascia and periosteum. Blood vessels and nerves are also present in this layer, which serves as a storage depot for lipid, an insulator to conserve body heat, and a protective cushion against trauma.

APPENDAGEAL STRUCTURES
Appendageal structures are derived from aggregates of epidermal cells that become specialized during early embryonic development. Small buds (primary epithelial germs) appear in the 3rd fetal mo and give rise to hair follicles, sebaceous and apocrine glands, and the attachment bulges for the arrector pili muscles. Eccrine sweat glands are derived from separate epidermal outgrowths that arise in the 2nd fetal mo and are completely formed by the 5th mo. Formation of nails is initiated in the 3rd intrauterine mo.

Hair Follicles
The pilosebaceous unit includes the hair follicle, sebaceous gland, arrector pili muscle, and, in areas such as the axillae, an apocrine gland. Hair follicles are distributed throughout the skin, except in the palms, soles, lips, and glans penis. Individual follicles extend from the surface of the epidermis to the deep dermis. The hair follicle is divided into 4 segments: the infundibulum, which extends from the skin surface to
the opening of the sebaceous duct; the isthmus, extending from the sebaceous duct opening to the bulge; the lower follicle between the bulge and the hair bulb; and the hair bulb. The bulge is at the insertion of the arrector pili muscle and is a focus of epidermal stem cells. The bulb is where the matrix cells and the dermal papilla are involved in formation and maintenance of the hair. The growing hair consists of the hair shaft, made of dead keratinocytes, and its supporting inner and outer root sheaths.

Human hair growth is cyclic, with alternate periods of growth (anagen), transition (catagen), and rest (telogen). The length of the anagen phase varies from months to years. At birth, all hairs are in the anagen phase. Subsequent generative activity lacks synchrony, so an overall random pattern of growth and shedding prevails. At any time, approximately 85% of hairs are in the anagen phase. Scalp hair usually grows about 1 cm per month.

The types of hair are lanugo, terminal, and vellus hairs. Lanugo hair is thin and short; this hair is shed in utero and is replaced by vellus hair by 36–40 wk of gestation. Vellus hair is short, soft, and frequently unpigmented and is distributed over the rest of the body. Terminal hair is long and coarse and is found on the scalp, beard, eyebrows, eyelashes, and axillary and pubic areas. During puberty, androgenic hormone stimulation causes pubic, axillary, and beard hair to change from vellus hair to terminal hair.

**Sebaceous Glands**

Sebaceous glands occur in all areas except the palms, soles, and dorsal feet and are most numerous on the face, upper chest, and back. Their ducts open into the hair follicles except on the lips, prepuce, and labia minora, where they emerge directly onto the mucosal surface. These holocrine glands are saccular structures that are often branched and lobulated and consist of a proliferative basal layer of small flat cells peripheral to the central mass of lipidized cells. The latter cells disintegrate as they move toward the duct and form the lipid secretion known as sebum, which consists of triglycerides, wax esters, squalene, and cholesterol esters. The purpose of sebum production likely relates to hydrophobic skin barrier function. Sebaceous glands depend on hormonal stimulation and are activated by androgens at puberty. Fetal sebaceous glands are stimulated by maternal androgens, and their lipid secretion, together with desquamated stratum corneum cells, constitutes the vernix caseosa.

**Apocrine Glands**

The apocrine glands are located in the axillae, areolae, perianal and genital areas, and the periumbilical region. These large, coiled, tubular structures continuously secrete an odorless milky fluid that is discharged in response to adrenergic stimuli, usually as a result of emotional stress. Bacterial biotransformation of apocrine sweat components (fatty acids, thioalcohols, and steroids) accounts for the unpleasant odor associated with perspiration. Apocrine glands remain dormant until puberty, when they enlarge and secretion begins in response to androgenic activity. The secretory coil of the gland consists of a single layer of cells enclosed by a layer of contractile myoepithelial cells. The duct is lined with a double layer of cuboidal cells and opens into the pilosebaceous complex. Although apocrine glands do not function in thermoregulation, they are involved in certain disease processes.

**Eccrine Sweat Glands**

Eccrine sweat glands are distributed over the entire body surface and are most abundant on the palms and soles. Those on the hairy skin respond to thermal stimuli and serve to regulate body temperature by delivering water to the skin surface for evaporation; in contrast, sweat glands on the palms and soles respond mainly to psychophysiological stimuli.

Each eccrine gland consists of a secretory coil located in the reticular dermis or subcutaneous fat and a secretory duct that opens onto the skin surface. Sweat pores can be identified on the epidermal ridges of the palm and fingers with a magnifying lens but are not readily visualized elsewhere. Two types of cells constitute the single-layered secretory coil: small dark cells and large clear cells. These rest on a layer of contractile myoepithelial cells and a basement membrane. The glands are supplied by sympathetic nerve fibers, but the pharmacologic mediator of sweating is acetylcholine rather than epinephrine. Sweat from these glands consists of water, sodium, potassium, calcium, chloride, phosphorus, lactate, and small quantities of iron, glucose, and protein. The composition varies with the rate of sweating but is always hypotonic in normal children.

**Nails**

Nails are specialized protective epidermal structures that form convex, translucent, tight-fitting plates on the distal dorsal surfaces of the fingers and toes. The nail plate, which is derived from a metabolically active matrix of multiplying cells situated beneath the posterior nail fold, is composed of anucleate keratinocytes. Nail growth is relatively slow; complete fingernail regrowth takes 6 mo, while complete toenail regrowth requires 12–18 mo. The nail plate is bounded by the lateral and posterior nail folds; a thin eponychium (the cuticle) protrudes from the posterior fold over a crescent-shaped white area called the lunula. The eponychium serves as a sealant barrier to protect the germinal matrix of the nail plate. The pink color beneath the nail reflects the underlying vascular bed. Nail health relies on several factors, including nutrition, hydration, local infection/irritation, and systemic disease.

*Bibliography is available at Expert Consult.*
Bibliography


HISTORY AND PHYSICAL EXAMINATION

Although many skin disorders are easily recognized by simple inspection, the history and physical examination are often necessary for accurate assessment. The skin examination should be performed under adequate illumination. In addition to the skin covering the entire body surface, mucous membranes (conjunctiva, oropharynx, nasal mucosa, anogenital mucosa), hair, and nails should be examined when appropriate. The color, turgor, texture, temperature, and moisture of the skin and the growth, texture, caliber, and luster of the hair and nails should be noted. Skin lesions should be palpated, inspected, and classified on the bases of morphology, size, color, texture, firmness, configuration, location, and distribution. One must also decide whether the changes are those of the primary lesion itself or whether the clinical pattern has been altered by a secondary factor such as infection, trauma, or therapy.

Primary lesions are classified as macules, papules, patches, plaques, nodules, tumors, vesicles, bullae, pustules, wheals, and cysts. A macule represents an alteration in skin color but cannot be felt. When the lesion is >1 cm, the term patch is used. Papules are palpable solid lesions <1 cm. Plaques are palpable lesions >1 cm in size and have a flat surface. Nodules are palpable lesions >1 cm with a rounded surface. The word tumor may be used for a large nodule that is suspected to be neoplastic in origin. Vesicles are raised, fluid-filled lesions <1 cm in diameter; when larger, they are called bullae. Pustules contain purulent material. Wheals are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collections of edema fluid. Cysts are circumscribed, thick-walled lesions; they are covered by a normal epidermis and contain fluid or semisolid material.

Primary lesions may change into secondary lesions, or secondary lesions may develop over time where no primary lesion existed.
Primary lesions are usually more helpful for diagnostic purposes than secondary lesions. Secondary lesions include scales, purpura, petechiae, ulcers, erosions, excoriations, fissures, crusts, and scars. Scales consist of compressed layers of stratum corneum cells that are retained on the skin surface. Purpura are the result of bleeding into the skin and have a red-purple color; they may be flat or palpable. Petechiae are small purpura <2-3 mm. Erosions involve focal loss of the epidermis, and they heal without scarring. Ulcers extend into the dermis and tend to heal with scarring. Ulcerated lesions inflicted by scratching are often linear or angular in configuration and are called excoriations. Fissures are caused by splitting or cracking. Crusts consist of matted, retained accumulations of blood, serum, pus, and epithelial debris on the surface of a weeping lesion. Scars are end-stage lesions that can be thin, depressed, and atrophic; raised and hypertrophic; or flat and pliable. Lichenification is a thickening of skin with accentuation of normal skin lines that is caused by chronic irritation (rubbing, scratching) or inflammation.

If the diagnosis is not clear after a thorough examination, 1 or more diagnostic procedures may be indicated.

**BIOPSY OF SKIN**

Biopsy of skin is occasionally required for diagnosis. Punch biopsy is a simple, relatively painless procedure and usually provides adequate tissue for examination if the appropriate lesion is sampled. The selection of a fresh, well-developed primary lesion is extremely important to obtain an accurate diagnosis. The site of the biopsy should have relatively low risk for damage to underlying dermal structures. After cleansing of the site, the skin is anesthetized by intradermal injection of 1-2% lidocaine, with or without epinephrine, with a 27- or 30-gauge needle. A punch, 3 or 4 mm in diameter, is pressed firmly against the skin and rotated until it sinks to the proper depth. All 3 layers (epidermis, dermis, subcutis) should be contained in the plug. The plug should be lifted gently with forceps or extracted with a needle and separated from the underlying tissue with iris scissors. Bleeding abates with firm pressure and with suturing. The biopsy specimen should be placed in 10% formaldehyde solution (Formalin) for appropriate processing.

**WOOD LAMP**

A Wood lamp emits ultraviolet light mainly at a wavelength of 365 nm. The examination, which is performed in a darkened room, is useful in accentuating changes in pigmentation and detecting fluorescence in certain infectious disorders. Discrete areas of altered pigment can often be visualized more clearly by using a Wood lamp, particularly if the pigmentary change is epidermal. Hyperpigmented lesions appear darker, and hypopigmented lesions (e.g., those seen in tuberous sclerosis), lighter than the surrounding skin. Blue-green fluorescence is detectable at the base of each infected hair shaft in ectothrix infections, which may appear pale yellow, but this color is not evidence of a fungal infection. Dermatophyte lesions of the skin (tinea corporis) do not fluoresce; macules of tinea versicolor have a yellow fluorescence under a Wood lamp. Erythrasma, an intertriginous infection caused by Corynebacterium minutissimum, may fluoresce pink-orange, whereas Pseudomonas aeruginosa is yellow-green under a Wood lamp.

**POTASSIUM HYDROXIDE PREPARATION**

Potassium hydroxide (KOH) preparation is a rapid and reliable method for detecting fungal elements of both yeasts and dermatophytes. Scaly lesions should be scraped at the active border for optimal recovery of mycelia and spores. Vesicles should be unroofed, and the blister roof should be clipped and placed on a slide for examination. In tinea capitis, infected hairs must be plucked from the follicle; scales from the scalp do not usually contain mycelia. A few drops of 20% KOH are added to the specimen. Dimethyl sulfoxide is usually in solution with the KOH, negating the need to heat the specimen. If using KOH without dimethyl sulfoxide, the specimen is gently heated over an alcohol lamp or on a hot plate until the KOH begins to bubble. Alternatively, sufficient time (10-20 min) can be allowed for dissolution of the keratin at room temperature. The preparation is examined under low-intensity light microscopy for fungal elements.

**TZANCK SMEAR**

Tzanck smear is useful in the diagnosis of infections caused by herpes simplex virus or varicella zoster virus and for the detection of acantholytic cells in pemphigus. An intact, fresh vesicle is ruptured and drained of fluid. The roof and base of the blister are then carefully scraped with a no. 15 scalpel blade, with care taken to avoid drawing a significant amount of blood; the material is smeared on a clear glass slide and air dried. Staining with Giemsa stain is preferable, but Wright stain is acceptable. Balloon cells and multinucleated giant cells are diagnostic of herpesvirus infection; acantholytic epidermal cells are characteristic of pemphigus.

Direct fluorescent assay and polymerase chain reaction tests have largely replaced Tzanck smears in the diagnosis of herpes simplex and varicella zoster infections. Both of these are rapid, sensitive, and specific, with the polymerase chain reaction even more so. When obtaining specimens for these tests, the vesicles should be ruptured prior to sample collection with the swab.

**IMMUNOFLUORESCENCE STUDIES**

Immunofluorescence studies of skin can be used to detect tissue-fixed antibodies to skin components and complement; characteristic staining patterns are specific for certain skin disorders (Table 645-1). Direct immunofluorescence detects autoantibodies bound to cutaneous antigens in the skin, while indirect immunofluorescence detects circulating autoantibodies present in the serum.

Skin biopsy specimens for direct immunofluorescence should be obtained from involved sites except in those diseases for which peripheral skin or uninvolved skin is required. A punch biopsy sample is obtained, and the tissue is placed in a special transport medium or immediately frozen in liquid nitrogen for transport or storage. Thin cryostat sections of the specimen are incubated with fluorescein-conjugated antibodies to the specific antigens.

Serum of patients can be examined by indirect immunofluorescence techniques using sections of normal human skin, guinea pig lip, or monkey esophagus as substrate. The substrate is incubated with fresh or thawed frozen serum and then with fluorescein-conjugated antihuman globulin. If the serum contains antibody to epithelial components, its specific staining pattern can be seen on fluorescence microscopy. By serial dilution, the titer of circulating antibody can be estimated.

**645.1 Cutaneous Manifestations of Systemic Diseases**

Brianne Z. Dickey and Yvonne E. Chiu

Selected diseases have signature skin findings, often as the presenting signs of illness, that can facilitate the assessment of patients with complex medical states (Table 645-2).

**CONNECTIVE TISSUE DISEASES**

**Lupus Erythematosus**

Lupus erythematosus (LE; see Chapter 158) is an idiopathic autoimmune inflammatory disease that may be multisystemic (i.e., systemic LE or SLE) or confined to the skin. Distinct cutaneous lupus subtypes seen in children include acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE (including discoid LE, discussed under “Discoid Lupus Erythematosus”), and neonatal LE (discussed under "Neonatal Lupus Erythematosus").

**Systemic Lupus Erythematosus**

SLE is a chronic inflammatory multisystem disease. It is diagnosed when 4 of 11 well-defined criteria are present (see Chapter 158). Three of the criteria are skin findings. Criterion 1 is the classic malar or “butterfly” rash (Fig. 645-1). It must be distinguished from other causes of a “red face,” most notably seborrheic dermatitis, atopic dermatitis, and...
Table 645-1  Immunofluorescence Findings in Immune-Mediated Cutaneous Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INVOLVED SKIN</th>
<th>UNINVOLVED SKIN</th>
<th>DIRECT IF FINDINGS</th>
<th>INDIRECT IF FINDINGS</th>
<th>CIRCULATING ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Negative</td>
<td>Positive</td>
<td>Granular IgA ± C in papillary dermis</td>
<td>None</td>
<td>IgA antiendomyosial and transglutaminase antibodies</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Positive</td>
<td>Positive</td>
<td>Linear IgG and C band in BMZ, occasionally IgM, IgA, IgE</td>
<td>IgG to BMZ</td>
<td>IgG anti-BP180 and anti-BP230</td>
</tr>
<tr>
<td>Pemphigus (all variants)</td>
<td>Positive</td>
<td>Positive</td>
<td>IgG in intercellular spaces of epidermis between keratinocytes</td>
<td>IgG to intercellular spaces of epidermis between keratinocytes</td>
<td>IgG antidesmoglein 1 and 3 (pemphigus vulgaris and foliaceus); IgA antidesmocollin 1 (IgA pemphigus)</td>
</tr>
<tr>
<td>Linear IgA bullous dermatosis (chronic bullous dermatosis of childhood)</td>
<td>Positive</td>
<td>Positive</td>
<td>Linear IgA at BMZ, occasionally C</td>
<td>Low titer, rare IgA, anti-BP180</td>
<td>None</td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
<td>Positive</td>
<td>Negative</td>
<td>Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)</td>
<td>None</td>
<td>Usually ANA-negative</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>Positive</td>
<td>Variable; exposed to sun, 30-50%; nonexposed, 10-30%</td>
<td>Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)</td>
<td>None</td>
<td>ANA Anti-Ro (SSA), anti-La (SSB) Anti-RNP Anti-dsDNA Anti-Sm</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Positive</td>
<td>Positive</td>
<td>IgA around vessel walls</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibody; BMZ, basement membrane zone at the dermal–epidermal junction; BP, bullous pemphigoid; C, complement; dsDNA, double-stranded deoxyribonucleic acid; IF, immunofluorescence; Ig, immunoglobulin; Sm, Smith; SSA/SSB, Sjögren syndrome A/B; RNP, ribonucleoprotein.

Rosacea. Criterion 2 is discoid lupus lesions. Criterion 3 is a photosensitive erythematous macular or papular eruption (Fig. 645-2). Other associated but not diagnostic cutaneous findings include purpura lesions, livedo reticularis, mucosal ulcerations, Raynaud phenomenon, urticaria, and nonscarring alopecia.

On histology, cutaneous LE demonstrates varying degrees of epidermal atrophy, plugging of hair follicles, and a vacuolar alteration at an inflamed dermal–epidermal junction. Deposition of immunoglobulins (IgM, IgG) and complement in lesional skin may help confirm the diagnosis. Immune deposits in nonlesional sun-exposed skin are found in the majority of patients with SLE (lupus band test), although clinical use of this test has been mostly abandoned in favor of serologic testing.

The skin lesions often respond to treatment of the SLE with systemic agents. Oral hydroxychloroquine is used most commonly, but many other systemic therapies are effective, including both classic and biologic immunosuppressants. Low- to mid-potency topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroid injection may be considered for adjunctive therapy.

Neonatal Lupus Erythematosus
Neonatal LE (see Chapter 158.1) manifests at birth or during the 1st few wk of life as annular, erythematous, scaly plaques, typically on the head, neck, and upper trunk (Fig. 645-3). Telangiectasias are also common. Ultraviolet light may exacerbate or initiate cutaneous lesions. Passive transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies causes the transient skin lesions, though most infants are born to mothers without a known rheumatologic diagnosis. Antibody levels wane by 6 mo, generally resulting in clearance of the rash. Congenital heart block occurs in 30% of affected infants, but only 10% of affected infants have both skin and cardiac abnormalities. Noncardiac extracutaneous manifestations, such as anemia, thrombocytopenia, and cholestatic liver disease are less common. Neonatal LE is often misdiagnosed as infantile eczema, seborrheic dermatitis, or tinea corporis. Skin lesions are typically managed conservatively given the transient nature of neonatal LE, and strict sun avoidance and protection are important. If necessary, low- to mid-potency topical corticosteroids may be used. Systemic agents should be avoided. Maternal antinuclear antibody testing is indicated.

Discoid Lupus Erythematosus
Discoid LE (DLE) is uncommon in early childhood and manifests in late adolescence. The signature skin findings in DLE are chronic, erythematous, scaly, atrophic plaques (Fig. 645-4) on sun-exposed skin that frequently heal with scarring and dyspigmentation. Extracutaneous features may include involvement of the nasal and oral mucosa, eyes, and nails. The differential diagnosis includes other photodermatoses, such as polymorphous light eruption, juvenile springtime eruption, and juvenile dermatomyositis. There is a distinct overlap between SLE and DLE, with common histopathologic features and photoexcitability; most patients with DLE have normal laboratory results and do not progress to systemic disease.

First-line treatment of DLE consists of low- to mid-potency topical corticosteroids. Other topical options include calcineurin inhibitors, retinoids, and topically-applied R-salbutamol. Intralesional corticosteroid injection is also effective for severe localized lesions. Oral hydroxychloroquine is used first-line for severe skin disease or as a second-line agent when lesions are not controlled with topical or local agents. Strict ultraviolet light avoidance is important.

Juvenile Dermatomyositis
Characteristic skin findings are often the presenting sign of juvenile dermatomyositis (JDM; see Chapter 159). An ill-defined, erythematous, scaly plaques overlying the knuckles and other joints (Gottron papules) are helpful in suggesting the diagnosis in the absence of associated muscle weakness (Fig. 645-5). Other cutaneous features include nail fold and gingival margin telangiectasia, palmar hyperkeratosis (“mechanic’s hands”),
### Table 645-2
Characteristics of Cutaneous Signs of Systemic Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>AGE OF ONSET</th>
<th>SKIN LESIONS</th>
<th>DISTRIBUTION</th>
<th>DIAGNOSTIC EVALUATIONS AND FINDINGS</th>
<th>ASSOCIATED SYMPTOMS/SIGNS</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Any</td>
<td>Erythematous patches, palpable purpura, livedo reticularis, Raynaud phenomenon, thrombocytopenic and nonthrombocytopenic purpura</td>
<td>Any</td>
<td>ANA panel, anti–dsDNA, Complement levels, Urinalysis</td>
<td>Photodistribution; malar face</td>
<td>Juvenile dermatomyositis, Drug eruption, Inflamed hemangiomatosis, Infantile hemangioma, Juvenile dermatomyositis, Subacute cutaneous lupus erythematosus</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>Childhood and adolescence</td>
<td>Aphthae; erythema nodosum, pyoderma gangrenosum, thrombophlebitis</td>
<td>Acral; diffuse</td>
<td>Skin biopsy, Liver function</td>
<td>Acral; diffuse</td>
<td>Drug eruption, Infectious exanthem</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Childhood and adolescence</td>
<td>Purpuric papules and plaques</td>
<td>Buttocks; lower extremities</td>
<td>Urinalysis, Blood urea nitrogen/creatinine ratio, Skin biopsy</td>
<td>Abdominal pain, Arthritis, Conjunctivitis, Flu-like illness</td>
<td>Infantile hemorrhagic edema, Viral exanthem, Kawasaki disease</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Newborn</td>
<td>Annular, scaly plaques, atopy, erythema nodosum</td>
<td>Head/neck</td>
<td>ANA, Anti-Ro (SSA), Anti-La (SSB)</td>
<td>Arthritis, Nephritis, Cerebritis, Serositis</td>
<td>Seborrheic dermatitis, Juvenile dermatomyositis, Drug eruption, Infectious exanthem</td>
</tr>
<tr>
<td>Juvenile dermatomyositis</td>
<td>Any</td>
<td>Erythematous to violaceous scaly, macules; discrete papules overlying knuckles</td>
<td>Shoulder girdle; extremities; knuckles; palms</td>
<td>ANA, AST, ALT, Aldolase, Creatine kinase, Lactate dehydrogenase, Creatine phosphokinase, Lactic dehydrogenase</td>
<td>Abdominal pain, Arthritis, Mucositis, Hepatitis</td>
<td>Abdominal pain, Arthritis, Conjunctivitis, Flulike illness, Mucositis, Hepatitis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Childhood and adolescence</td>
<td>Priapic papules and plaques</td>
<td>Buttocks; lower extremities</td>
<td>Skin biopsy, Liver function</td>
<td>Abdominal pain, Arthritis, Conjunctivitis, Flu-like illness</td>
<td>Vasculitis, Drug eruption, Infantile hemorrhagic edema, Kawasaki disease</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Childhood and adolescence</td>
<td>Aphthae; erythema nodosum, pyoderma gangrenosum, thrombophlebitis</td>
<td>Oral ulcers, perianal fissures</td>
<td>Skin biopsy, Liver function</td>
<td>Acral; diffuse</td>
<td>Drug eruption, Infectious exanthem, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Sweet syndrome</td>
<td>Any</td>
<td>Infiltrated erythematous, edematous plaques</td>
<td>None</td>
<td>Skin biopsy, ESR</td>
<td>Head and neck, palms/soles, diffuse</td>
<td>Fever, Mucositis, Hepatitis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>Any</td>
<td>Acute: erythema, papules, vesicles, bulla</td>
<td>None</td>
<td>Skin biopsy, Liver function</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Serum sickness–like reaction (SSLR)</td>
<td>Any</td>
<td>Erythema; urticarial macules and plaques</td>
<td>Acral; diffuse</td>
<td>Skin biopsy, ESR</td>
<td>Acral; diffuse</td>
<td>None</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibodies; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; SSA/SSB, Sjögren’s syndrome A/B.
ulceration resulting from vasculopathy or underlying calcinosis, lipo-
dystrophy, and a poikilodermatus (dyspigmentation and telangiecta-
sia) eruption over the shoulder girdle ("shawl sign"). Cutaneous
features may precede the systemic illness, which is primarily character-
ized by muscle weakness and pain. The differential diagnosis includes
atopic dermatitis, other connective tissue diseases, lichen planus,
medication reactions, and infectious exanthems. Lesional skin
demonstrates epidermal atrophy and vacuolar degeneration at the
dermal-epidermal junction, often similar to LE. JDM is distinct from
adult dermatomyositis in both presentation and prognosis. Pediatric
patients have more difficulty with gastrointestinal vasculopathy and
cutaneous calcifications, and JDM is not a paraneoplastic phenomenon
as in adults. A rare clinical variant known as amyopathic dermato-
myositis occurs when only skin, and not muscle, is involved.

Skin lesions benefit from systemic immunosuppressive therapy as
discussed in detail in Chapter 159. Additional treatment options for
localized skin disease include topical corticosteroids and calcineurin
inhibitors. In case reports, the cutaneous calcinosis of JDM has been
difficult to manage with a variety of agents, and no treatment consen-
sus exists. Strict photoprotection and sunlight avoidance are vital to
prevent cutaneous exacerbations.

**Systemic Sclerosis**

Systemic sclerosis frequently manifests as acral (sclerodactyly, ulcer-
ation, nail fold telangiectasia, or Raynaud phenomenon) and facial
changes (pinched nose, furrowed perioral skin, or "scleroderma facies")
(see Chapter 160). Overlap syndromes such as *mixed connective
tissue disease* may include some physical and laboratory features of
scleroderma.

**VASCULITIDES**

The vasculitides (see Chapter 167) encompass a broad group of
disorders having considerable overlap with connective tissue diseases.
Immune-mediated inflammation of blood vessels of varying size
may be caused by an underlying inflammatory state, infection, medica-
tion, or malignancy. Common clinical features include palpable
Inflammatory Bowel Disease

Inflammatory bowel disease includes ulcerative colitis (see Chapter 336.1) and Crohn disease (see Chapter 336.2). Skin lesions of inflammatory bowel disease are classified as specific or reactive. Specific cutaneous manifestations have the same histologic features and pathologic mechanism as the underlying inflammatory bowel disease lesions and include aphthous ulcers, perianal fistulas and fissures, and metastatic Crohn disease (discussed below). Reactive cutaneous manifestations occur secondary to immune-mediated antigen cross-reactivity between gut and skin components; examples include erythema nodosum and pyoderma gangrenosum.

Up to 30% of patients with ulcerative colitis present with cutaneous manifestations. Aphthous ulcers are common and may worsen with gastrointestinal exacerbations. Erythema nodosum, occurring in up to 10% of patients, manifests as warm, erythematous nodules, often on the distal lower extremities. Pyoderma gangrenosum is a focal, ulcerative process that has distinctive, inflamed, undermined borders and a purulent, boggy center. Thrombophlebitis also occurs at an increased rate in patients with ulcerative colitis.

Crohn disease classically manifests as periannal fissures and skin tags, abscesses, sinuses, and fistulas; these may be presenting signs. A cobblestone appearance of oral mucosa may also be present. As in ulcerative colitis, aphthae, erythema nodosum, and pyoderma gangrenosum occur at increased frequency and may improve with treatment of the underlying disease. Noncaseating granulomatous inflammation is seen on routine histopathology, and when found in skin not contiguous with the intestinal tract, is labeled metastatic Crohn disease. Metastatic lesions may appear as solitary or multiple, localized plaques or nodules and may be located on perianal, perioral, or other cutaneous surfaces, including scars and ileostomy sites. In most cases of inflammatory bowel disease–associated skin disease, treatment of the underlying condition improves the cutaneous sequelae. Azathioprine, a common treatment, causes increased risk for nonmalignoma skin cancers.

Cutaneous Manifestations of Malignancy

Skin disease associated with malignancy has a wide variety of presentations, including both metastatic lesions and nonmalignant paraneoplastic conditions. Cutaneous metastases manifest as firm nodules and occur at any cutaneous site. Paraneoplastic reaction patterns are often distinctive and can aid in the diagnosis of the underlying malignancy. Some genetic syndromes have an increased malignancy risk that may be suggested initially by cutaneous signs. Other cutaneous findings that may signal an underlying malignancy include pruritus, ichthyosis, acanthosis nigricans, urticaria, pemphigus, and erythroderma.

Sweet Syndrome

Also known as acute febrile neutrophilic dermatosis, Sweet syndrome (see Chapter 169) occurs in several forms, including classical (usually idiopathic or infection-related, Fig. 645-7), malignancy-associated, immunodeficiency-related, and drug-induced; pathogenesis
Suspect medications include rash onset relative to exposure, character used in immunosuppressed patients. Features that may help identify suspect medication may be difficult owing to the many medications cutaneous eruptions of little clinical consequence. Identifying the Medication Reactions confounding.

CUTANEOUS REACTIONS IN THE SETTING OF IMMUNOSUPPRESSION Medication reactions, infectious etiologies, and graft-versus-host disease (GVHD) are included in the differential diagnosis in immunosuppressed patients; cutaneous and histologic similarities can be confounding.

Medication Reactions The majority of medication reactions are mild morbilliform or exanthematous eruptions of little clinical consequence. Identifying the suspect medication may be difficult owing to the many medications used in immunosuppressed patients. Features that may help identify suspect medications include rash onset relative to exposure, character of distribution and spread, associated symptoms, and laboratory data. Medication eruptions begin on the trunk 7–10 days after exposure; they spread peripherally and are associated with pruritus and, less commonly, with fever, arthralgia, and lymphadenopathy. Eosinophilia may support a diagnosis of drug eruption but may be absent in the setting of bone marrow suppression. Penicillins, sulfa drugs, cephalosporins, nonsteroidal antiinflammatory drugs, anticonvulsants, and aminoglycosides are common offenders. Medication eruptions may resolve despite continued use of the offending agent, or they may progress to more severe involvement. A careful drug history, elimination of all nonessential, suspect medications or change to medications of a similar class, and treatment of pruritus with emollients, topical steroids, antihistamines, and antipruritics are indicated. Skin biopsies are rarely useful in distinguishing medication eruptions from infectious exanthems, although GVHD, if sufficiently advanced, may have signature histopathologic findings.

Graft-Versus-Host Disease GVHD (see Chapter 137) may have florid cutaneous expression in addition to characteristic extracutaneous features such as fever, mucositis, diarrhea, and hepatitis. It may be either acute or chronic. Acute GVHD occurs in 20–70% of hematopoietic stem cell transplants, depending on histocompatibility differences. It may be mistaken for a medication reaction or infectious exanthem because of the nonspecific erythematous maculopapular (morbilliform) eruption that often starts focally and then generalizes. Features that suggest acute GVHD include timing of eruption (typically 1–3 wk after transplantation, at the time of hematopoietic reconstitution), initial involvement of the head and neck including the ears, and subsequent spread to the trunk, extremities, palms, and soles. In severe cases of acute GVHD, blistering, necrosis, and erythroderma occur. Chronic GVHD occurs in approximately 65% of long-term transplant survivors who may or may not have experienced prior acute GVHD. Cutaneous manifestations of chronic GVHD are distinctive, with sclerotic, poikilodermic scaly plaques and lichen planus-like papules predominating on the trunk and distal extremities (Fig. 645-8). Sclerotic areas are prone to contracture and chronic wound development. Involvement of the hair, nails, and oral mucosa is also common in chronic GVHD. First-line treatment for GVHD includes systemic glucocorticoids and other immunosuppressants supplemented by mid- to high-potency topical corticosteroids. In mild disease, topical corticosteroids or topical calcineurin inhibitors alone may be effective. Second-line treatment approaches include phototherapy (narrow band UVB or UVA1) and extracorporeal photopheresis. All patients with GVHD benefit from sunlight protection, emollient use, and topical or oral antipruritics.

Bibliography is available at Expert Consult.
Chapter 645  Evaluation of the Patient

Bibliography


645.2 Multisystem Medication Reactions

Brianne Z. Dickey and Yvonne E. Chiu

See also Chapter 152.

Most cutaneous reactions that result from the use of systemic medications are confined to the skin and resolve without sequelae after discontinuation of the offending agent (Table 645-3). More severe drug eruptions may be life-threatening, making rapid recognition vital (see Chapter 654). Genetics and, particularly, ethnicity appear to play a major role in determination of the occurrence of multisystem medication reactions, particularly to anticonvulsants.

**DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME)**

DRESS syndrome, or drug rash with eosinophilia and systemic symptoms, is also called drug hypersensitivity syndrome or anticonvulsant hypersensitivity syndrome. It is classically seen 2-6 wk after initial exposure to an anticonvulsant (carbamazepine, phenobarbital, phenytoin, lamotrigine) or other drugs (allopurinol, minocycline, sulfonamides [dapsone, sulfasalazine], other antibiotics) and often manifests as the triad of fever, rash, and hepatitis. The skin rash is initially located on the head, upper trunk, and arms. A diffuse exanthem of pruritic, morbilliform papules is most common, though any morphology may be present (Fig. 645-9). Exfoliation early in the course, as seen in toxic epidermal necrolysis, is uncommon. If mucous membrane involvement occurs, it is usually mild. Prominent periorcular or facial edema, cervical lymphadenopathy, pharyngitis, and malaise accompany this dramatic cutaneous eruption. Eosinophilia (≥500/µL) and atypical lymphocytosis are common but not always present. Hepatitis ranging from mild elevation of liver transaminase values to frank hepatic failure may also be accompanied by interstitial nephritis, pneumonitis, myocarditis, shock, and encephalitis; mortality rate from these complications approaches 10%. Late-onset thyroiditis and hypothyroidism may occur months later as a result of antimicrosomal antibodies directed against thyroid peroxidases involved in drug metabolism.

The proposed pathogenesis of anticonvulsant-induced DRESS syndrome relates to a heritable defect in the epoxide hydrolase pathway leading to accumulation of toxic metabolites and subsequent...

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<table>
<thead>
<tr>
<th>Table 645-3</th>
<th>Drug Eruptions in Pediatric Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERUPTION</strong></td>
<td><strong>KEY DRUGS</strong></td>
</tr>
<tr>
<td>Urticaria</td>
<td>Penicillins, cephalosporins, sulfonamides, aspirin/NSAIDs, radiocontrast media, TNF inhibitors</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Aspirin/NSAIDs, angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>Serum sickness–like reaction</td>
<td>Cephalosporins, penicillins, minocycline, bupropion, sulfonamides</td>
</tr>
<tr>
<td>Exanthematous</td>
<td>Any drug</td>
</tr>
<tr>
<td>Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)</td>
<td>Phenytoin, phenobarbital, carbamazepine, lamotrigine, allopurinol, sulfonamides, dapsone, minocycline</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>Captopril, enalapril, β-blockers, gold salts, hydrochlorothiazide, hydroxychloroquine, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs</td>
</tr>
<tr>
<td>Fixed drug</td>
<td>Sulfonamides, ibuprofen, acetaminophen, tetracyclines, pseudoephedrine, barbiturates, lamotrigine, metronidazole, penicillin</td>
</tr>
<tr>
<td>Pustular (acute generalized exanthematous pustulosis)</td>
<td>β-Lactam antibiotics, macrolides, clindamycin, terbinafine, calcium channel blockers, antimalarials</td>
</tr>
<tr>
<td>Acneiform</td>
<td>Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, tetracycline, B vitamins, azathioprine</td>
</tr>
<tr>
<td>Pseudoporphyria</td>
<td>NSAIDs, cytochrome oxidase-2 inhibitors, tetracyclines, furosemide</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Penicillins, NSAIDs, sulfonamides, cephalosporins</td>
</tr>
<tr>
<td>Stevens-Johnson/toxic epidermal necrolysis</td>
<td>Sulfonamides, anticonvulsants, NSAIDs, allopurinol, dapsone</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>Minocycline, procainamide, hydralazine, isoniazid, penicillamine, carbamazepine, chlorpromazine, infliximab</td>
</tr>
</tbody>
</table>

NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor.

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Serum Sickness-Like Reaction

Serum sickness-like reaction (SSLR) manifests as annular, urticarial, sharply margined, coalescing plaques; these often have a lavender hue to the center. In addition, acral erythema/edema, arthritis/arthralgia, lymphadenopathy, and fever are often present. Unlike with true serum sickness (see Chapter 150), laboratory evidence of circulating immune complexes and multisystem involvement of vasculitis are typically absent. The differential diagnosis includes Kawasaki disease, connective tissue diseases, acute annular urticaria, and DRESS syndrome. SSLR is most commonly seen after exposure to various drugs (especially cefaclor and other antibiotics), as well as after certain infections and vaccinations. The cause of drug-related SSLR is unknown, but a toxic metabolite is suspected. In contrast to DRESS syndrome, SSLR typically occurs after repeated drug exposures. Medication withdrawal and symptomatic treatment with oral antihistamines and analgesics are recommended. Systemic glucocorticoids are indicated for severe joint involvement or extensive rashes.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis is often drug-related (most commonly aminopenicillins, macrolides, sulfonamides), occurring within hours to days after drug exposure. It is characterized by many nonfollicular sterile pustules with underlying edema and erythema, typically beginning on the face and intertriginous regions (Fig. 645-10). Neutrophilia and fever are common, whereas eosinophilia is less common than in DRESS syndrome. The rash may burn or itch; mucous membrane involvement is rare and often mild. Internal organ involvement is not common and often is asymptomatic. A pustular smear is always indicated to rule out infection in the setting of leukocytosis, fever, and a pustular rash. Therapy consists of stopping the causative drug and offering symptomatic relief with moist dressings, emollients, and mid-potency topical corticosteroids (applied twice daily for 1 wk).

Bibliography is available at Expert Consult.
Bibliography


Chapter 646
Principles of Therapy
Stephen R. Humphrey and Beth A. Drolet

Competent skin care requires an appreciation of primary vs secondary lesions, a specific diagnosis, and knowledge of the natural course of the disease. If the diagnosis is uncertain, it is better to err on the side of less-aggressive rather than more-aggressive treatment.

In the use of topical medication, consideration of vehicle is as important as the specific therapeutic agent. Acute weeping lesions respond best to wet compresses, followed by lotions or creams. For dry, thickened, scaly skin, or for treatment of a contact allergic reaction possibly the consequence of a component of a topical medication, an ointment base is preferable, as it helps to occlude and moisten the affected area. Gels and solutions are most useful for the scalp and other hairy areas because of their faster absorption. The site of involvement is of considerable importance because the most desirable vehicle may not be cosmetically or functionally appropriate, such as an ointment on the face or hands. A patient’s preference should also play a part in the choice of vehicle because compliance is poor if a medication is not acceptable to a patient. Ointments tend to sting less and are the least irritating. Cosmetically acceptable foam delivery systems have been developed, and the number of products and formulations available is increasing.

Most lotions are mixtures of water and oil that can be poured. After the water evaporates, the small amount of remaining oil covers the skin. Some shake lotions are a suspension of water and insoluble powder; as the water evaporates, cooling the skin, a thin film of powder covers the skin. Creams are emulsions of oil and water that are viscous and do not pour (more oil than in lotions). Ointments have oils and a small amount of water or no water at all; they feel greasy, lubricate dry skin, trap water, and aid in occlusion. Ointments without water usually require no preservatives because microorganisms require water to survive. Because of this, ointments often have the lowest number and concentration of ingredients, decreasing the risk of sensitizing the skin.

Therapy should be kept as simple as possible, and specific written instructions about the frequency and duration of application should be provided. Physicians should become familiar with one or two preparations in each category and should learn to use them appropriately. Prescribing nonspecific proprietary medications that may contain sensitizing agents should be avoided. Certain preparations, such as topical antihistamines and sensitizing anesthetics, are never indicated.

WET DRESSINGS
Wet dressings cool and dry the skin by evaporation and cleanse it by removing crusts and exudate, which would cause further irritation if permitted to remain. The dressings decrease pruritus, burning, and stinging sensations and are indicated for acutely inflamed moist or oozing dermatitis. Although various astringent and antiseptic substances may be added to the solution, cool or tepid tap water compresses are just as effective. Dressings of multiple layers of Kerlix, gauze, or soft cotton material may be saturated with water and remoistened as often as necessary. Compresses should be applied for 10-20 min at least every 4 hr and should usually be continued for 24-48 hr.

Alternatively, cotton long johns can be soaked in water and then wrung as dry as possible. These are placed on the child and covered with dry pajamas, preferably sleeper pajamas with feet. The child should sleep in these overnight. This type of dressing can be used nightly for up to 1 wk.

Wet dressings or wet wraps in conjunction with topical steroids may also be used in more severe cases of dermatitis (e.g., atopic dermatitis). In this method, a thin layer of the topical steroid is applied to the affected areas, which are then covered with warm, wet wraps for approximately 30 min to 1 hr 2-3 times daily. This method is especially effective in children with extensive and severe dermatitis.

BATH OILS, COLOIDS, SOAPS
Bath oil has little benefit in the treatment of children. It offers little moisturizing effect but increases the risk of injury during a bath. Bath oil may lubricate the surface of the bathtub, causing an adult or child to fall when stepping into the tub. Tar bath solutions can be prescribed and may be helpful for psoriasis and atopic dermatitis. Colloids such as starch powder and colloidal oatmeal are soothing and antipruritic for some patients when added to the bathwater. Oilated colloidal oatmeal contains mineral oil and lanolin derivatives for lubrication if the skin is dry. These can also lubricate the bathtub surface. Ordinary bath soaps may be irritating and drying if patients have dry skin or dermatitis. Synthetic soaps are much less irritating. Fragrance-free soaps and cleansers are often better tolerated and less likely to irritate skin. When skin is acutely inflamed, avoidance of soap is advised.

LUBRICANTS
Lubricants, such as lotions, creams, and ointments, can be used as moisturizers for dry skin and as vehicles for topical agents such as corticosteroids and keratolytics. In general, ointments are the most effective emollients. Numerous commercial preparations are available. Some patients do not tolerate ointments, and some may be sensitized to a component of the lubricant; some preservatives in creams are also sensitizers. These preparations can be applied several times a day if necessary and tolerated. Maximal effect is achieved when they are applied to dry skin 2 or 3 times daily. Lotions containing menthol and camphor in an emollient vehicle can help control pruritus and dryness, but the use of moisturizers in addition to these products is best to decrease skin dryness.

SHAMPOOS
Special shampoos containing sulfur, salicylic acid, zinc, and selenium sulfide are useful for conditions in which there is scaling of the scalp, such as seborrheic dermatitis or psoriasis. Tar-containing shampoos are useful in these conditions. Most shampoos also contain surfactants and detergents. They should be used as frequently as necessary to control scaling. Patients should be instructed to leave the lathered shampoo in contact with the scalp for 5-10 minutes before thorough rinsing.

SHAKE LOTIONS
Shake lotions are useful antipruritic agents; they consist of a suspension of powder in a liquid vehicle. Water-dispersible oil may be added for lubrication. These preparations can be used effectively in combination with wet dressings for exudative dermatitis. Cooling occurs as the lotion evaporates and the powder deposited on the skin absorbs moisture.

POWders
Powders are hygroscopic and serve as absorptive agents in areas of excessive moisture. When dry, powders decrease friction between 2 surfaces. They are most useful in the intertriginous areas and between the toes, where maceration and abrasion may result from friction on movement. Coarse powders may cake; therefore, they should be of fine particle size and inert, unless medication has been incorporated in the formulation. The use of cornstarch-based powders in inflamed or broken skin may serve as a good growth environment for microorganisms and should be avoided.

PASTES
Pastes contain fine powder in ointment vehicles and are not often prescribed in current dermatologic therapy; in certain situations, however, they can be used effectively to protect vulnerably or damaged skin. A stiff zinc oxide paste is bland and inert and can be applied to the diaper area to prevent further irritation due to diaper dermatitis. Zinc oxide paste should be applied in a thick layer completely
obscuring the skin and is removed more easily with mineral oil than with soap and water.

KERATOLYTIC AGENTS
Urea-containing agents are hydrophilic; they hydrate the stratum corneum and make the skin more pliable. In addition, because urea dissolves hydrogen bonds and epidermal keratin, it is effective in treating scaling disorders. Concentrations of 10–40% are available in several commercial lotions and creams, which can be applied once or twice daily as tolerated. Salicylic acid is an effective keratolytic agent and can be incorporated into various vehicles in concentrations up to 6% to be applied 2 or 3 times daily. Salicylic acid preparations should not be used in treating small infants or on large surface areas or denuded skin; percutaneous absorption may result in salicylism. The α-hydroxy acids, particularly lactic acid and glycolic acid, are available in commercial preparations or can be incorporated in an ointment vehicle in concentrations up to 12%. Some creams contain both urea and lactic acid. The α-hydroxy acid preparations are useful for the treatment of keratinizing disorders and may be applied once or twice daily. Some patients complain of burning with the use of these agents; in such cases, the frequency of application should be decreased.

TAR COMPOUNDS
Tars are obtained from bituminous coal, shale, petrolatum (coal tars), and wood. They are antipruritic and astringent and appear to promote normal keratinization. They may be useful for chronic eczema and psoriasis, and their efficacy may be increased if the affected area is exposed to UV light after the tar has been removed. Tars should not be used for acute inflammatory lesions. Tars are often messy and unacceptable because they may stain and they have an odor. They may be incorporated into shampoos, bath oils, lotions, and ointments. A useful preparation for pediatric patients is liquor carbonis detergens 2–5% in a cream or ointment vehicle. Tar gel and tar in light body oil are relatively pleasant cosmetic preparations that cause minimal staining of skin and fabrics. Tars can also be incorporated into a vehicle with a topical corticosteroid. The frequency of application varies from 1–3 times daily, according to tolerance. Many children refuse to use tar preparations because of their odor and staining characteristics.

ANTIFUNGAL AGENTS
Antifungal agents are available as powders, lotions, creams, and ointments for the treatment of dermatophyte and yeast infections. Nystatin, naftifine, and amphoterin B are specific for Candida albicans and are ineffective in other fungal disorders. Tolnaftate is effective against dermatophytes but not against yeast. The spectrum for ciclopirox olamine includes the dermatophytes, Malassezia furfur, and C. albicans. The azoles clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, and sulconazole have a similar broad spectrum. Butenafine has a similar broad spectrum and also has antifungal properties. Terbinafine has greater activity against dermatophytes but poorer activity against yeasts than the azoles. The topical antifungal agents should be applied 1–2 times a day for most fungal infections. All have low sensitizing potential; additives such as preservatives and stabilizers in the vehicles may cause allergic contact dermatitis. Ointments containing 6% benzoic acid and 3% salicyclic acid are potent keratolytic agents that have also been used for the treatment of dermatophyte infections. Irritant reactions are common.

TOPICAL ANTI​B​IOTICS
Topical antibiotics have been used for many years to treat local cutaneous infections, although their efficacy, with the exception of mupirocin, fusidic acid and retapamulin, has been questioned. Ointments are the preferred vehicles (except in the treatment of acne vulgaris; see Chapter 609) and combinations with other topical agents such as corticosteroids are, in general, inadvisable. Whenever possible, the etiologic agent should be identified and treated specifically. Antibiotics in wide use as systemic preparations should be avoided because of the risk of bacterial resistance. The sensitizing potential of certain topical antibiotics, such as neomycin and nitrofurazone, should be kept in mind and avoided when possible. Mupirocin, fusidic acid, and retapamulin are the most effective topical agents currently available and are as effective as oral erythromycin in treatment of mild to moderate impetigo. Polysporin and bacitracin are not as effective.

TOPICAL CORTICOSTEROIDS
Topical corticosteroids are potent antiinflammatory agents and effective antipruritic agents. Successful therapeutic results are achieved in a wide variety of skin conditions. Corticosteroids can be divided into 7 different categories on the basis of strength (Table 646-1), but for practical purposes, 4 categories can be used: low, moderate, high, and super. Low-potency preparations include hydrocortisone, deonide, and hydrocortisone butyrate. Medium-potency compounds include amcinonide, betamethasone, flurandrenolide, fluocinolone, mometa-sone furoate, and triamcinolone. High-potency topical steroids include fluocinonide and halcinonide. Betamethasone dipropionate and clobetasol propionate are superpotent preparations and should be prescribed with care. Some of these compounds are formulated in several strengths according to clinical efficacy and degree of vasoconstriction. Physicians using topical steroids should become familiar with preparations within each class.

All corticosteroids can be obtained in various vehicles, including creams, ointments, solutions, gels, and aerosols. Some are available in a foam vehicle. Absorption is enhanced by an ointment or gel vehicle, but the vehicle should be selected on the basis of the type of disorder and the site of involvement. Frequency of application should be determined by the potency of the preparation, the location on the body, and the severity of the eruption. Applying a thin film 2 times daily usually suffices. Adverse local effects include cutaneous atrophy, striae, telangiectasia, acneiform eruptions, purpura, hypopigmentation, and increased hair growth. Systemic adverse effects of high-potency and superpotent topical steroids occur with long-term use and include poor growth, cataracts, and suppression of adrenal function.

<table>
<thead>
<tr>
<th>CLASS</th>
<th>POTENCY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS 1—SUPERPOTENT</td>
<td>Betamethasone dipropionate, 0.05% gel, ointment</td>
<td></td>
</tr>
<tr>
<td>CLASS 2—POTENT</td>
<td>Betamethasone dipropionate cream, 0.05%</td>
<td>Desoximetasone cream, ointment, gel 0.05% and 0.25%</td>
</tr>
<tr>
<td>CLASS 3—UPPER MID-STRENGTH</td>
<td>Betamethasone dipropionate cream, 0.05%</td>
<td>Betamethasone valerate ointment, 0.1%</td>
</tr>
<tr>
<td>CLASS 4—MID-STRENGTH</td>
<td>Desoximetasone cream, 0.05%</td>
<td>Fluocinolone acetonide ointment, 0.025%</td>
</tr>
<tr>
<td>CLASS 5—LOWER MID-STRENGTH</td>
<td>Betamethasone valerate cream/lointment, 0.1%</td>
<td>Fluocinolone acetonide cream, 0.025%</td>
</tr>
<tr>
<td>CLASS 6—MILD STRENGTH</td>
<td>Desonide cream, 0.05%</td>
<td>Fluocinolone acetonide cream, 0.025%</td>
</tr>
<tr>
<td>CLASS 7—LEAST POTENT</td>
<td>Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone</td>
<td></td>
</tr>
</tbody>
</table>

The relative skin thickness should be considered in regard to the selection of class of steroid (see Table 646-1). Thin skin such as the eyelids, face, groin, and genitalia will absorb a substantial amount of medication compared to the thickest skin on the palms and soles. One adult fingertips worth of medication is enough to cover an area the size of an adult palm and is approximately half a gram of medication. Knowing the area being treated and which medication class to prescribe can decrease potential for side effects.

In selected circumstances, corticosteroids may be administered by intraleisional injection (acne cysts, keloids, psoriatic plaques, alopecia areata, persistent insect bite reactions). Only experienced physicians should use this method of administration.

**TOPICAL NONSTEROIDAL ANTIINFLAMMATORY AGENTS**
Calcineurin-inhibiting antiinflammatory agents that inhibit T-cell activation may be used instead of topical steroids for the treatment of atopic dermatitis and other inflammatory conditions. These agents are pimecrolimus and tacrolimus. They do not have the adverse local effects seen with topical steroid. Stinging with application is the most common complaint and may be lessened by mixing the medication with an ointment such as petrolatum jelly for the initial applications. These agents are only as strong as medium-potency topical steroids. They should be used with caution owing to evidence from animal experiments and case reports of an increased risk of lymphoma.

**SUNSCREENS**
Sunscreens are of 2 general types: (1) those, such as zinc oxide and titanium dioxide, that absorb all wavelengths of the UV and visible spectrums; and (2) a heterogeneous group of chemicals that selectively absorb energy of various wavelengths within the UV spectrum. In addition to the spectrum of light that is blocked, other factors to be considered include cosmetic acceptance, sensitizing potential, retention on skin while swimming or sweating, required frequency of application, and cost. Sunscreen ingredients include para-aminobenzoic acid (PABA) with ethanol, PABA esters, cinnamates, and benzophenone. These block transmission of the majority of solar UVB and some UVA wavelengths. Avobenzone and ecamisule are more effective in blocking UVA. Antioxidants may also be found in some sunscreens. Lip protectants that absorb in the UVB range are also available. Sunscreens are designated by sun protection factor (SPF). The SPF is defined as the amount of time to develop a mild sunburn with the sunscreen compared with the amount of time without the sunscreen. A minimum SPF factor of 15 is required for most fair-skinned individuals to prevent sunburn; however, an SPF of 30 should be recommended most often. The higher the SPF, the better the protection is against UVB rays. Sunscreens do not include any measurement of the efficacy in blocking UVA. The efficacy of these agents depends on careful attention to instructions for use. Chemical sunscreens should be applied at least 30 min before sun exposure to permit penetration into the epidermis, again on arrival at the destination, and every subsequent hour when exposed to direct sunlight. Most patients with photosensitivity eruptions require protection by agents that absorb both UVB and UVA wavelengths (see Chapter 656).

Although sunscreens do confer photoprotection and may decrease the development of nevi, protection is incomplete against all harmful UV light. Midday (10 AM to 4 PM) sun avoidance is the primary method of photoprotection. Clothing, hats, and staying in the shade offer additional sun protection.

**LASER THERAPY**
The vascular-specific pulsed dye laser therapy is used mainly for the treatment of capillary malformations (port-wine stains). Spider telangiectasia, small facial pyogenic granulomas, superficial and ulcerated hemangioma, and warts may also be treated. Vascular-specific pulsed dye lasers produce light that is readily absorbed by oxyhemoglobin, producing selective photothermolysis of vascular lesions.

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


Minor evanescent lesions of newborn infants, particularly when florid, may cause undue concern. Most of the entities are relatively common, benign, and transient and do not require therapy.

**SEBACEOUS HYPERPLASIA**
Minute, profuse, yellow-white papules are frequently found on the forehead, nose, upper lip, and cheeks of a term infant; they represent hyperplastic sebaceous glands (Fig. 647-1). These tiny papules diminish gradually in size and disappear entirely within the 1st few wk of life.

**MILIA**
Milia are superficial epidermal inclusion cysts that contain laminated keratinized material. The lesion is a firm cyst, 1-2 mm in diameter, and pearly, opalescent white. Milia may occur at any age but in neonates are most frequently scattered over the face and gingivae and on the midline of the palate, where they are called *Epstein pearls*. Milia exfoliate spontaneously in most infants and may be ignored; those that appear in scars or sites of trauma in older children may be gently unroofed and the contents extracted with a fine-gauge needle.

**SUCKING BLISTERS**
Solitary or scattered superficial bullae present at birth on the upper limbs of infants at birth are presumably induced by vigorous sucking on the affected part in utero. Common sites are the radial aspect of the forearm, thumb, and index finger. These bullae resolve rapidly without sequelae and should be distinguished from sucking pads (calluses), which are found on the lips in the 1st few mo and are a result of combined intracellular edema and hyperkeratosis. The diagnosis can be confirmed by observing the neonate sucking the affected area.

**CUTIS MARMORATA**
When a newborn infant is exposed to low environmental temperatures, an evanescent, lacy, reticulated red and/or blue cutaneous vascular

*Figure 647-1* Sebaceous hyperplasia. Minute white-yellow papules on the nose of a newborn.
Dermal melanocytosis, which appears as blue or slate-gray macular lesions, has variably defined margins. It occurs most commonly in the presacral area but may be found over the posterior thighs, legs, back, and shoulders (Fig. 647-3). The spots may be solitary or numerous and often involve large areas. The incidence of these lesions varies widely across ethnicities, being most common in African-American, Asian, and Hispanic infants (25-80% depending on the study) and less common in white infants (around 6%). The peculiar hue of these macules is a result of the dermal location of melanin-containing melanocytes (mid-dermal melanocytosis) that are presumably arrested in their migration from neural crest to epidermis. They usually fade during the 1st few yr of life as a result of darkening of the overlying skin. Malignant degeneration does not occur. The characteristic appearance and congenital onset distinguish these spots from the bruises of child abuse. Rarely Mongolian spots are associated with Hurler syndrome or GM1 gangliosidosis type 1.

Erythema toxicum
A benign, self-limited, evanescent eruption, erythema toxicum occurs in approximately 50% of full-term infants; preterm infants are affected less commonly. The lesions are firm, yellow-white, 1-2 mm papules or pustules with a surrounding erythematous flare (Fig. 647-4). At times, splotchy erythema is the only manifestation. Lesions may be sparse or numerous and either clustered in several sites or widely dispersed over much of the body surface. The palms and soles are usually spared. Peak incidence occurs on the 2nd day of life, but new lesions may erupt during the 1st few days as the rash waxes and wanes. Onset may occasionally be delayed for a few days to weeks in premature infants. The pustules form below the stratum corneum or deeper in the epidermis and represent collections of eosinophils that also accumulate around the upper portion of the pilosebaceous follicle. The eosinophils can be demonstrated in Wright-stained smears of the intralesional contents. Cultures are sterile.

The cause of erythema toxicum is unknown. The lesions can mimic pyoderma, candidiasis, herpes simplex, transient neonatal pustular melanosis, and miliaria but can be differentiated by the characteristic infiltrate of eosinophils and the absence of organisms on a stained smear. The course is brief, and no therapy is required. Incontinentia pigmenti and eosinophilic pustular folliculitis also have eosinophilic
of epidermal cells. Cultures and smears can be used to distinguish these pustules from those of pyoderma and erythema toxicum, because the lesions of pustular melanosis do not contain bacteria or dense aggregates of eosinophils. No therapy is required.

**INFANTILE ACROPUSTULOSIS**

Onset of infantile acropustulosis generally occurs at 2-10 mo of age; lesions are occasionally noted at birth. Darkly pigmented males have a predisposition, but infants of both sexes and all races may be affected. The cause is unknown.

The lesions are initially discrete erythematous papules that become vesiculopustular within 24 hr and subsequently crust before healing. They are intensely pruritic. Preferred sites are the palms of the hands and the soles and sides of the feet, where the lesions may be extensive. A less dense eruption may be found on the dorsum of the hands and feet, ankles, and wrists. Pustules occasionally occur elsewhere on the body. Each episode lasts 7-14 days, during which time pustules continue to appear in crops. After a 2-4 wk remission, a new outbreak follows. This cyclic pattern continues for approximately 2 yr; permanent resolution is often preceded by longer intervals of remission between periods of activity. Infants with acropustulosis are otherwise well.

Wright-stained smears of intralesional contents show abundant neutrophils or, occasionally, a predominance of eosinophils. Histologically, well-circumscribed, subcorneal, neutrophilic pustules, with or without eosinophils, are noted.

The **differential diagnosis** in neonates includes transient neonatal pustular melanosis, erythema toxicum, milia, cutaneous candidiasis, and staphylococcal pustulosis. In older infants and toddlers, additional diagnostic considerations include scabies, dyshidrotic eczema, pustular psoriasis, subcorneal pustular dermatosis, and hand-foot-and-mouth disease. A therapeutic trial of a scabicide is warranted in equivocal cases.

**Therapy** is directed at minimizing discomfort for infants. Topical corticosteroid preparations and/or oral antihistamines decrease the severity of the pruritus and an infant’s irritability. Dapsone (2 mg/kg/day taken orally twice daily) is effective but has potentially serious side effects—notably, hemolytic anemia and methemoglobinemia—and should be used with caution.

**EOSINOPHILIC PUSTULAR FOLLICULITIS**

Eosinophilic pustular folliculitis is defined as recurrent crops of pruritic, coalescing, follicular papulopustules on the face, trunk, and extremities. Fifty percent of patients have peripheral eosinophilia with eosinophil counts exceeding 5%, and approximately 30% have leukocytosis (>10,000 leukocytes/mm³).

Infants account for <10% of all cases of eosinophilic pustular folliculitis. The clinical and histologic appearances of this disorder in infants closely resemble those in immunocompetent adults, with minor exceptions. In infants, the lesions are most prominent on the scalp, although they also occur on the trunk and extremities and occasionally are found on the palms and soles. The classic annular and polycyclic appearance with centrifugal enlargement is not seen in infants. Adults have an eosinophilic infiltrate that invades sebaceous glands and the outer root sheath of hair follicles, often leading to spongiosis in the outer root sheath. The eosinophilic infiltrate in most infants, however, is perifollicular, without spongiosis in the outer root sheath. Because of the slight differences between clinical findings and course in immunocompetent adults, immunocompromised adults and those in infants, it has been proposed that eosinophilic pustular folliculitis be subclassified into classic, HIV-related, and infantile forms. The **differential diagnosis** includes erythema toxicum neonatorum, infantile acropustulosis, localized pustular psoriasis, pustular folliculitis, and transient neonatal pustular melanosis.

High-potency or superpotent topical corticosteroids are the most effective treatment (see Table 646-1 in Chapter 646).

*Bibliography is available at Expert Consult.*
Bibliography


SKIN Dimples
Cutaneous depressions over bony prominences and in the acral area, at times associated with pits and creases, may occur in normal children and in association with dysmorphologic syndromes. Skin dimples may develop in utero as a result of interposition of tissue between a sharp bony point and the uterine wall, which leads to decreased subcutaneous tissue formation.

Dimples may also be present overlying an area of bone hypoplasia. Bilateral acromial skin dimples are usually an isolated finding, but they are also seen in association with deletion of the long arm of chromosome 18. Dimples tend to occur over the patella in congenital rubella, over the lateral aspects of the knees and elbows in prune-belly syndrome, on the pretrivial surface in campomelic dwarfs, and in the shape of an H on the chin in whistling-face syndrome.

Sacral dimples are common and usually are isolated findings. They may be seen in multiple syndromes or in association with spina bifida occulta and diastomelia. Association with a mass or other cutaneous stigma (hair, aplasia cutis, lipoma, hemangioma) should increase concern for underlying spinal dysraphism (see Chapter 391). Ultrasonography during the 1st 3 mo of life, before ossification of the posterior elements of the lower spine, may provide a cost-effective, noninvasive method of assessing any associated lumbosacral spine abnormalities in infants with an isolated sacral dimple. Nonetheless, MRI of the spine is indicated if there is a strong suspicion of a spinal dysraphism.

REDUNDANT SKIN
Loose folds of skin may be differentiated from a congenital defect of elastic tissue or collagen such as cutis laxa, Ehlers-Danlos syndrome, or pseudoxanthoma elasticum. Redundant skin over the posterior part of the neck is common in the Turner, Noonan, Down, and Klippel-Feil syndromes and monosomy 1p36; more generalized folds of skin occur in infants with trisomy 18 and short-limbed dwarfism.

AMNIOTIC CONstriction BANDS
Partial or complete constriction bands that produce defects in extremities and digits are found in 1 in 10,000-45,000 otherwise normal infants. Constrictive tissue bands are caused by primary amniotic rupture, with subsequent entanglement of fetal parts, particularly limbs, in shrunken fibrotic amniotic strands. This event is probably sporadic, with negligible risk of recurrence. Formation of constrictive tissue bands is associated with abdominal trauma, amniocentesis, and hereditary defects of collagen such as Ehlers-Danlos syndrome and osteogenesis imperfecta.

Adhesive bands involve the craniofacial area and are associated with severe defects such as encephalocoele and facial clefts. Adhesive bands result from broad fusion between disrupted fetal tissue and an intact amniotic membrane. The craniofacial defects appear not to be caused by constrictive amniotic bands but to result from a vascular disruption sequence with or without cephaloamniotic adhesion (see Chapter 108).

The limb–body wall complex involves vascular disruption early in development, affecting several embryonic structures; it includes at least 2 of the following 3 characteristics: exencephaly or encephalocoele with facial clefts, thoracocoeis to and abdominoschisis, and limb defects.

PREAURICULAR SINUSES AND PITS
Pits and sinuses anterior to the pinna may be a result of imperfect fusion of the tubercles of the 1st and 2nd branchial arches. These anomalies may be unilateral or bilateral, may be familial, are more common among females and African-Americans, and at times are associated with other anomalies of the ears and face. Preauricular pits are present in branchiootorenal dysplasia 1 syndrome (EYA-1 gene), an autosomal dominant disorder that consists of external ear malformations, branchial fistulas, hearing loss, and renal anomalies. When the tracts become chronically infected, retention cysts may form and drain intermittently; such lesions may require excision.

ACCESSORY TRAGI
An accessory tragus typically appears as a single pedunculated, flesh-colored papule in the preauricular region anterior to the tragus. Less commonly, accessory tragi are multiple or bilateral, and may be located in the preauricular area, on the cheek along the line of the mandible (Fig. 648-1), or on the lateral aspect of the neck anterior to the sternocleidomastoid muscle. In contrast to the rest of the pinna, which develops from the 2nd branchial arch, the tragus and accessory tragi derive from the 1st branchial arch. Accessory tragi may occur as isolated defects or in chromosomal 1st branchial arch syndromes that include anomalies of the ears and face, such as cleft lip, cleft palate, and mandibular hypoplasia. An accessory tragus is consistently found in occuloauriculovertebral syndrome (Goldenhar syndrome). Surgical excision is appropriate.

BRANCHIAL CLEFT AND THYROGLOSSAL CYSTS AND SINUSES
Cysts and sinuses in the neck may be formed along the course of the 1st, 2nd, 3rd, or 4th branchial clefts as a result of improper closure during embryonic life. Second branchial cleft cysts are the most common. The lesions may be unilateral or bilateral (2-3%) and may open onto the cutaneous surface or drain into the pharynx. Secondary infection is an indication for systemic antibiotic therapy. These anomalies may be inherited as autosomal dominant traits.

ThyroGLOSSAL cysts and fistulas are similar defects located in or near the midline of the neck; they may extend to the base of the tongue. A pathognomonic sign is vertical motion of the mass with swallowing and tongue protrusion. In nearly 50% of affected children, the cyst or fistula manifests as an infected midline upper neck mass. Cysts in the tongue base may be differentiated from an undescended lingual thyroid by radionuclide scanning. Unlike branchial cysts, a thyroglossal duct cyst often appears after an upper respiratory infection (see Chapter 563).

SUPERNUMERARY NIPPLES
Solitary or multiple accessory nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. They are more common among African-American (3.5%) than white (0.6%) children. Accessory nipples may or may not
have areolae and may be mistaken for congenital nevi. They may be excised for cosmetic reasons. Renal or urinary tract anomalies and hematologic abnormalities may rarely occur in children with this finding (see Chapter 551).

APLASIA CUTIS CONGENITA (CONGENITAL ABSENCE OF SKIN)

Developmental absence of skin is usually noted on the scalp as multiple or solitary (70%), noninflammatory, well-demarcated, oval or circular 1–2 cm ulcers (Table 648-1). The appearance of lesions varies, depending on when they occurred during intrauterine development. Those that form early in gestation may heal before delivery and appear as atrophic, fibrotic scars with associated alopecia, whereas more recent defects may manifest as ulcerations. Most occur at the vertex of the scalp just lateral to the midline, but similar defects may also occur on the face, trunk, and limbs, where they are often symmetric and usually associated with an intrauterine fetal demise of a twin (fetus papyraceus). The depth and size of the ulcer varies. Only the epidermis and upper dermis may be involved, resulting in minimal scarring or hair loss, or less often the defect may extend to the deep dermis, to the subcutaneous tissue, and, rarely, to the periosteum, skull, and dura. Lesions may be surrounded by a collar of hair (Fig. 648-2).

Diagnosis is made on the basis of physical findings indicative of in utero disruption of skin development. Lesions are sometimes mistakenly attributed to scalp electrodes or obstetric trauma. Most are sporadic, but autosomal dominant and recessive cases occur as well; some are due to mutations in BMS1, a ribosomal guanosine triphosphatase.

Although most individuals with aplasia cutis congenita have no other abnormalities, these lesions may be associated with isolated physical anomalies or with malformation syndromes, including Opitz, Adams-Oliver, ocucocerebrocutaneous, Johanson-Blizzard, and 4p(−), X-p22 microdeletion syndromes, trisomy 13-15, and chromosome 16-18 defects (see Table 648-1). Aplasia cutis congenita may also be found in association with an overt or underlying embryologic malformation, such as meningomyelocele, gastroschisis, omphalocele, or spinal dysraphism. Aplasia cutis congenita in association with fetus papyraceus is apparently caused by ischemic or thrombotic events in the placenta and fetus. Blistering or skin fragility and/or absence or deformity of nails in association with aplasia cutis congenita is a well-recognized manifestation of epidermolysis bullosa.

Major complications are rare and more often associated with large, stellate lesions of the midline parietal scalp. Hemorrhage, secondary local infection, and meningitis have been reported. If the defect is small, recovery is uneventful, with gradual epithelialization and formation of a hairless atrophic scar over a period of several weeks. Small bony defects usually close spontaneously in the 1st yr of life. Large or numerous scalp defects may require repair, but care must be taken as abnormal underlying venous structures have complicated surgical repair. Truncal and limb defects, despite being large, usually epithelialize and form atrophic scars, which can later be revised.

FOCAL FACIAL DERMAL DYSPLASIAS

The focal facial dermal dysplasias (FFDDs) are a rare group of conditions sharing bitemporal or preauricular lesions resembling scars or aplasia cutis congenita. FFDD1 (Brauer syndrome) is inherited in an autosomal dominant fashion and typically mild associated facial features. FFDD2 (Brauer-Setleis syndrome) and FFDD3 (Setleis syndrome) are associated with thin, puckered periorbital skin, distichiasis and/or absent eyelashes, upslating palpebral fissures, flat nasal bridge, large lips and redundant facial skin. FFDD2 is inherited in an autosomal dominant fashion whereas FFDD3 is autosomal recessive and caused by mutations in TWIST2. FFDD4 has no other related skin findings; it is inherited both in autosomal dominant and recessive manners and is caused by mutations in CYP26C1.

FOCAL DERMAL HYPOPLASIA (GOLTZ SYNDROME)

A rare congenital mesoectodermal and ectodermal disorder, focal dermal hypoplasia is characterized by dysplasia of connective tissue in the skin and skeleton. This disorder is an X-linked dominant disorder caused by mutations in the PORCN gene. It manifests as numerous soft tan papillomas. Other cutaneous findings include linear atrophic

Table 648-1

<table>
<thead>
<tr>
<th>GROUP</th>
<th>DEFINITION</th>
<th>INHERITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isolated scalp involvement; may be associated with single defects</td>
<td>AD</td>
</tr>
<tr>
<td>2</td>
<td>Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocoele</td>
<td>AD</td>
</tr>
<tr>
<td>3</td>
<td>Scalp ACC with epidermal nevus</td>
<td>Sporadic</td>
</tr>
<tr>
<td>4</td>
<td>ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocoele</td>
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<td>ACC with placental infarcts, and/or fetus papyraceus</td>
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</tr>
<tr>
<td>6</td>
<td>ACC with epidermolysis bullosa</td>
<td>AD or AR</td>
</tr>
<tr>
<td>7</td>
<td>ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet</td>
<td>AD or AR</td>
</tr>
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<td>8</td>
<td>ACC caused by teratogens (e.g., varicella, herpes, methimazole)</td>
<td>Sporadic</td>
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<td>9</td>
<td>ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p−, deletion Xp22.1, ectodermal dysplasia, Johanson-Blizzard syndrome, Adams-Oliver syndrome)</td>
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ACC, Aplasia cutis congenital; AD, autosomal dominant; AR, autosomal recessive.


Figure 648-2 Solitary scalp vertex lesion of aplasia cutis congenita with hair collar.
lesions; reticulated hypopigmentation and hyperpigmentation; telangiectasias; congenital absence of skin; angiofibromas presenting as verrucous excrences; and papillomas of the lips, tongue, circumoral region, vulva, anus, and the inguinal, axillary, and periumbilical areas. Partial alopecia, sweating disorders, and dystrophic nails are additional, less common ectodermal anomalies. The most frequent skeletal defects are syndactyly, clinodactyly, polydactyly, and scoliosis. Osteopathia striata are fine parallel vertical stripes noted on radiographs in the metaphyses of long bones of patients with this disorder; these are highly characteristic of focal dermal hypoplasia but are not pathognomonic. Many ocular abnormalities, the most common of which are colobomas, strabismus, nystagmus, and microphthalmia, are also characteristic. Small stature, dental defects, soft tissue anomalies, and peculiar dermatoglyphic patterns are also common. Cognitive impairment occurs occasionally.

**DYSKERATOSIS CONGENITA (ZINSSER-ENGMAN-COLE SYNDROME)**

Dyskeratosis congenita, a rare familial syndrome, consists classically of the triad of reticulated hyperpigmentation of the skin (Fig. 648-3), dystrophic nails, and mucous membrane leukoplakia in association with immunologic and hematologic abnormalities. Patients with dyskeratosis congenita also show signs of premature aging and increased occurrence of cancer, especially squamous cell carcinoma. Dyskeratosis congenita may be X-linked recessive (DKC-1 gene), autosomal dominant (hTERC and TINF2 genes), or autosomal recessive (NOLA3 gene). Onset occurs in childhood, most commonly as nail dystrophy. The nails become atrophic and ridged longitudinally with progression to pterygia and complete nail loss. Skin changes usually appear after onset of nail changes and consist of reticulated gray-brown pigmentation, atrophy, and telangiectasia, especially on the neck, face, and chest. Hyperhidrosis and hyperkeratosis of the palms and soles, sparse scalp hair, and easy blistering of the hands and feet are also characteristic. Blepharitis, ectropion, and excessive tearing because of atresia of the lacrimal ducts are occasional manifestations. Oral leukokeratosis may give rise to squamous cell carcinoma. Other mucous membranes, including conjunctival, urethral, and genital, may be involved. Infection, malignancy, pulmonary fibrosis and bone marrow failure are common, and death before age 40 yr is typical.

**CUTIS VERTICIS GYRATA**

Cutis verticis gyrata, an unusual alteration of the scalp that is more common in males, may be present from birth or may develop during adolescence. The scalp is characterized by convoluted elevated folds, 1-2 cm in thickness, usually in the fronto-occipital axis. Unlike the lax skin of other disorders, the convolutions cannot generally be flattened by traction. Primary cutis gyrata may be associated with intellectual disability, retinitis pigmentosa, sensorineural deafness, and thyroid aplasia. Secondary cutis gyrata may be due to chronic inflammatory diseases, tumors, nevi, and acromegaly.

*Bibliography is available at Expert Consult.*
Bibliography


Ectodermal dysplasia (ED) is a heterogeneous group of disorders characterized by a constellation of findings involving defects of 2 or more of the following: teeth, skin, and appendageal structures including hair, nails, and eccrine and sebaceous glands. Although more than 150 EDs have been described, the majority are rare.

**HYPOHIDROTIC ECTODERMAL DYSPLASIA**

The syndrome known as hypohidrotic ectodermal dysplasia (HED) manifests as a triad of defects: partial or complete absence of sweat glands, anomalous dentition, and hypotrichosis. There are 4 recognized types of HED (Table 649-1); HED-1 (X-linked recessive) is most common.

In HED, affected patients are unable to sweat and may experience episodes of high fever in warm environments, which may be mistakenly considered to be fevers of unknown origin. This error is particularly common in infancy, when the facial changes are not easily appreciated. Diagnosis at this time may be made using the starch-iodine test or palmar or scalp biopsy. Scalp biopsy is the most sensitive and is 100% specific. The typical facies are characterized by frontal bossing; malar hypoplasia; a flattened nasal bridge; recessed columella; thick, everted lips; wrinkled, hyperpigmented periorbital skin; and prominent, low-set ears (Fig. 649-1). The skin over the entire body is dry, finely wrinkled, and hypopigmented, often with a prominent venous pattern. Extensive peeling of the skin is a clinical clue to diagnosis in the newborn period. The paucity of sebaceous glands may account for the dry skin. The scalp hair is sparse, fine, and lightly pigmented, and eyebrows and lashes are sparse or absent. Other body hair is also sparse or absent. Sexual hair growth is normal. Anodontia or hypodontia with widely spaced, conical teeth is a consistent feature (Fig. 649-1). Otolaryngic and ophthalmologic abnormalities secondary to decreased saliva and tear production are seen. The incidence of atopic diseases in children with HED is high. Gastroesophageal reflux is common and may play a role in failure to thrive, which is seen in 20% of cases. Sexual development is usually normal. Historically, the infant mortality rate has been 30%. Carrier females of X-linked HED have no or variable clinical manifestations.

Hypohidrotic ED with immune deficiencies causes similar findings in sweating and hair and nail development, in association with a dysgammaglobulinemia. Significant mortality is seen from recurrent infections.

**Treatment** of children with HED includes protecting them from exposure to high ambient temperatures. Early dental evaluation is necessary so that prostheses can be provided for cosmetic reasons and for adequate nutrition. The use of artificial tears prevents damage to the cornea in patients with defective lacrimation. Alopecia may necessitate the wearing of a wig to improve appearance.
Hypohidrotic ectodermal dysplasia is characterized by pointed ears, fine hair, periorbital hyperpigmentation, midfacial hypoplasia, and pegged teeth. (Courtesy of the Fitzsimons Army Medical Center teaching file.)

### Table 649-1

<table>
<thead>
<tr>
<th>TYPE</th>
<th>INHERITANCE</th>
<th>GENE DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED-1</td>
<td>X-linked recessive</td>
<td>Ectodysplasin A (EDA)</td>
</tr>
<tr>
<td>ED-2</td>
<td>Autosomal recessive</td>
<td>Ectodysplasin A anhidrotic receptor (EDAR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDAR-associated death gene (EDARADD)</td>
</tr>
<tr>
<td>ED-3</td>
<td>Autosomal dominant</td>
<td>EDAR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDARADD</td>
</tr>
<tr>
<td>ED-anhidrotic with immune deficiency</td>
<td>Autosomal dominant</td>
<td><em>iKγ</em> (NEMO)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NFκB-1A</td>
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HIDROTIC ECTODERMAL DYSPLASIA (CLOUSTON SYNDROME)

The salient features of the autosomal dominant disorder hidrotic ED are dystrophic, hypoplastic, or absent nails; sparse hair; and hyperkeratosis of the palms and soles. Conjunctivitis and blepharitis are common. The dentition and sweating are always normal. Absence of eyebrows and eyelashes and hyperpigmentation over the knees, elbows, and knuckles have been noted in some affected individuals. Mutations in the *GJB6* gene encoding the gap junction protein connexin 30 are responsible for this disorder. A similar disorder associated with deafness has been described with mutations in the *GJB2* gene encoding the connexin 26 protein.

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


Nearly all vascular lesions of childhood may be divided into vascular malformations and vascular tumors (Table 650-1). Vascular malformations are developmental errors in blood vessel formation. Malformations do not regress but slowly enlarge. They should be named after the predominant vessel(s) forming the lesion. Genetic disorders may involve arterial, capillary, lymph, or venous malformations. Vascular tumors exhibit endothelial cell hyperplasia and proliferation.

**VASCULAR MALFORMATIONS**

**Capillary Malformation (Port-Wine Stain)**

Capillary malformations (CMs) are present at birth. These vascular malformations consist of mature dilated dermal capillaries. The lesions are macular, sharply circumscribed, pink to purple, and tremendously varied in size (Fig. 650-1). The head and neck region is the most common site of predilection; most lesions are unilateral. The mucous

<table>
<thead>
<tr>
<th>Table 650-1</th>
<th>International Society for the Study of Vascular Anomalies (ISSVA) Classification System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VASCULAR MALFORMATION</strong></td>
<td><strong>VASCULAR TUMOR</strong></td>
</tr>
<tr>
<td>Slow-flow malformations</td>
<td>Infantile hemangioma</td>
</tr>
<tr>
<td>Capillary malformation</td>
<td>Congenital hemangioma</td>
</tr>
<tr>
<td>Venous malformation</td>
<td>Rapidly involuting congenital hemangioma</td>
</tr>
<tr>
<td>Lymphatic malformation</td>
<td>Noninvoluting congenital hemangioma</td>
</tr>
<tr>
<td>Fast-flow malformations</td>
<td>Kaposiform hemangioendothelioma</td>
</tr>
<tr>
<td>Arterial malformation</td>
<td>Tufted angiomata</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>Spindle cell hemangioendothelioma</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>Epithelioid hemangioendothelioma</td>
</tr>
<tr>
<td>Combined vascular malformations</td>
<td>Other rare hemangioendotheliomas</td>
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<tr>
<td></td>
<td>Angiosarcoma</td>
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<tr>
<td></td>
<td>Acquired vascular tumors: pyogenic granuloma</td>
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</tbody>
</table>

Figure 650-1 Capillary malformation. Pink macule on the cheek of an infant.
membranes can be involved. As a child matures into adulthood, the CM may become darker in color and pebbly in consistency; it may occasionally develop elevated areas that bleed spontaneously.

True CM should be distinguished from nevus simplex, which, in contrast, is a relatively transient lesion often located in the midline (see Chapter 647). When a CM is lateral and localized to the forehead, and upper eyelid the diagnosis of Sturge-Weber syndrome (glaucoma, leptomeningeal venous angioma, seizures, hemiparesis) may be considered (see Chapter 596.3). Early screening for glaucoma is important to prevent additional damage to the eye. CMs also occur as a component of Klippel-Trenaunay syndrome and with moderate frequency in other syndromes, including Cobb (spinal arteriovenous malformation, port-wine stain), Proteus, Beckwith-Wiedemann, and Bonnet-Dechaume-Blanc syndromes. In the absence of associated anomalies, morbidity from these lesions may include a poor self-image, hypertrophy of underlying structures, and traumatic bleeding. In contrast to unilateral lesions associated with Sturge-Weber syndrome, medial frontofacial CMs are bilateral and involve the forehead, glabella, upper eyelids, nose, philtrum, and upper lip. These lesions may be familial, complete (involving all 7 areas), or incomplete, and are associated with other CMs on the occiput, neck or lumbosacral areas. Atypical cases are associated with Beckwith-Wiedemann and Rubinstein-Taybi syndromes.

The most effective treatment for CM is with the pulsed-dye laser. This therapy is targeted to hemoglobin within the lesion and avoids thermal injury to the surrounding normal tissue. After such treatment, the texture and pigmentation of the skin are generally normal without scarring. Therapy can begin in infancy, when the surface area of involvement is smaller. There may be advantages to treating within the 1st yr of life. Although this approach is quite effective, redarkening of the stain may occur 10 yr after therapy. Masking cosmetics may also be used.

**Angiokeratoma Circumscriptum**

Several forms of angiokeratoma have been described. Angiokeratomas are characterized by ectasia of superficial lymphatic vessels and capillaries with hyperkeratosis of the overlying epidermis. Angiokeratoma circumscriptum is a rare disorder consisting of a solitary lesion or multiple lesions that manifest as a plaque or plaques of blue-red crusted papules or nodules. The limbs are the sites of predilection. If therapy is desired, surgical excision is the treatment of choice.

**Venous Malformation**

Venous malformations include vein-only malformations and combination malformations. Malformations consisting of veins only run the gamut from nodules containing a mass of venules (Fig. 650-2) to diffuse large vein abnormalities that may consist of either a superficial component resembling varicose veins, deeper venous malformations, or both. Most venous malformations are sporadic, although inherited forms exist as well. Inherited forms and up to 40% of sporadic venous malformations are caused by TIE2 mutations. Treatment is reserved for painful or symptomatic lesions. Surgical excision is best for small or superficial nodular lesions and sclerotherapy or laser ablation is used for larger, diffuse lesions. Localized intravascular coagulopathy can be problematic in these lesions because of the chronic slow flow. This leads to both painful thrombotic episodes and the risk of progression to systemic disseminated intravascular coagulopathy.

**Cutis Marmorata Telangiectatica Congenita**

Cutis marmorata telangiectatica congenital is a benign vascular anomaly that represents dilation of superficial capillaries and veins and is apparent at birth. Involved areas of skin have a reticulated red or purple hue that resembles physiologic cutis marmorata but is more pronounced and relatively unvarying (Fig. 650-3). The lesions may be restricted to a single limb and a portion of the trunk or may be more widespread. The lesions become more pronounced during changes in environmental temperature, physical activity, or crying. In some cases, the underlying subcutaneous tissue is atrophic, and ulceration may occur within the reticulated bands. Rarely, defective growth of bone and other congenital abnormalities may be present. No specific therapy is indicated. Mild vascular-only cases may show gradual improvement. Cutis marmorata telangiectatica congenital may be associated with CM, Adams-Oliver syndrome, patent ductus arteriosus, and a variety of other anomalies. It must be differentiated from reticulate CM and physiologic cutis marmorata.

**Blue Rubber Bleb Nevus Syndrome**

Blue rubber bleb nevus is a rare syndrome consisting of numerous venous malformations of the skin, mucous membranes, and gastrointestinal tract. Typical lesions are blue-purple and rubbery in consistency; they vary in size from a few millimeters to a few centimeters in diameter. They are sometimes painful or tender. The nodules occasionally are present at birth but usually are progressive during childhood. New lesions may continue to develop throughout life. Large disfiguring and irregular blue marks may also occur. The lesions, which can rarely be located in the liver, spleen, and central nervous system in addition to the skin and gastrointestinal tract, do not involute spontaneously. Recurrent gastrointestinal hemorrhage due to lesions in the gastrointestinal tract may lead to severe anemia. Palliation can be achieved by excision of involved bowel.

**KLIPPEL-TRENAUNAY AND PARKES-WEBER SYNDROMES**

Klippel-Trenaunay syndrome is a term historically used to describe complex, mixed vascular malformation with overgrowth of bone and
Artérioveneuses malformations

AVMs are direct connections of artery to vein that bypass the capillary bed (Fig. 650-5). AVMs of the skin are very rare. Skin changes are often noted at birth, but they tend to be very subtle presenting as a red-pink patch. Over time the lesions deepen in color and often result in thickening of the skin and surrounding tissue. They are diagnosed from their obvious arterial palpation. Some AVMs are progressive and can lead to significant morbidity and even mortality, so early diagnosis and evaluation by an experienced multidisciplinary team is essential.

Phacomatoses pigmentovasculaires

Phacomatoses pigmentovasculaires is a rare disorder characterized by the association of a capillary malformation and melanocytic lesions. Typically, the capillary malformation is extensive, and associated pigmentary lesions may include dermal melanocytosis (mongolian spots), café-au-lait macules, or a nevus spilus (speckled nevus). Nonpigmented skin lesions that may occur in this setting include nevus anemicus and epidermal nevi. Systemic anomalies are seen in rare cases.

Nevus anemicus

Although present at birth, nevus anemicus may not be detectable until early childhood. The nevus consists of solitary or numerous, sharply delineated pale macules or patches that are most often on the trunk but may also occur on the neck or limbs. These nevi may simulate plaques of vitiligo, leukoderma, or nevoid pigmented defects, but they can be readily distinguished because of their response to firm stroking. Stroking evokes an erythematous line and flare in normal surrounding skin, but the skin of a nevus anemicus does not redden. They can also be diagnosed by diascopy, in which pressure of the skin with a glass slide will obscure the borders of a nevus anemicus. Although the cutaneous vasculature appears normal histologically, the blood vessels within the nevus do not respond to injection of vasodilators. It has been postulated that the persistent pallor may represent a sustained localized adrenergic vasoconstriction.

Vascular tumors

Vascular tumors include infantile hemangiomas, tufted angiomas, kaposiform hemangioendotheliomas, rapidly involuting congenital hemangiomas, and noninvoluting congenital hemangiomas.

Infantile hemangioma

Infantile hemangiomas (IHs) are proliferative, benign vascular tumors of vascular endothelium that may be present at birth or, more commonly, may become apparent in the first 2 weeks of life, predictably enlarge, and then spontaneously involute. IHs are the most common tumor of infancy, occurring in 5% of newborns. Risk factors include prematurity, low birthweight, female sex, and white race. IHs should be classified as superficial, deep, or mixed. The terms strawberry and cavernous should not be used to describe hemangiomas. The immunohistochemical marker GLUT-1 is specifically expressed in an IH, which helps distinguish it histologically from other vascular anomalies. Superficial IHs are bright red, protuberant, compressible, sharply demarcated lesions that may occur on any area of the body (Figs. 650-6 and 650-7). Although sometimes present at birth, they more often appear in the first 2 months of life and are heralded by an erythematous or blue mark on an area of pallor, which subsequently develops a fine telangiectatic pattern before the growth phase. The presenting sign may occasionally be an ulceration of the perineum or lip. Favored sites are the face, scalp, back, and anterior chest; lesions may be solitary or multiple. Patterns of facial involvement include frontotemporal, maxillary, mandibular, and frontonasal regions. IHs that are more deeply situated are more diffuse and are less defined than superficial IHs. The lesions are cystic, firm, or compressible, and the overlying skin may appear normal in color or may have a bluish hue (Fig. 650-8).
involvement, but lip lesions seem to persist most often. Complications include impairment of a vital function, ulceration, secondary infection, and permanent disfigurement (Table 650-2). The location of a lesion may interfere with a vital function (e.g., on eyelid interfering with vision, on urethra with urination, on airway with respiration). IHs in a "beard" distribution may be associated with upper airway or subglottic involvement. Stridor should suggest a tracheobronchial lesion. Large visceral IHs may be complicated by coexistent hypothyroidism because of type 3 iodothyronine deiodinase, and symptoms may be difficult to detect in this age group. Table 650-3 lists other concerning features.

In the usual patient with an IH who has no serious complications or extensive growth resulting in tissue destruction and severe disfigurement, treatment consists of expectant observation. Because almost all lesions regress spontaneously, therapy is rarely indicated. Parents require repeated reassurance and support. After spontaneous involution, many patients are left with small cosmetic defects, such as telangiectasia, hypopigmentation, fibrofatty deposits, and scars if the lesion has ulcerated. Residual telangiectasias may be treated with pulsed-dye laser therapy. Other defects can be treated or minimized by judicious surgical repair if desired.

In the rare case in which intervention is required, topical timolol solution (0.5% gel; maximum dose 0.5 mg/day) is effective, especially in small, superficial, nonulcerating and nonmucosal IH. At this time, topical timolol treatment appears a very safe alternative to observation alone for a superficial IH. Timolol solution may also be used with caution in the treatment of an ulcerated IH, with or without occlusion.

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The dose should be decreased gradually, though most patients may be evident after 2-4 weeks. Termination of growth and sometimes regression of hemangiomas may be seen. Steroids may be used. Termination of growth and sometimes regression of hemangiomas may be seen.

(cimetidine, ciprofloxacin, isoniazid, ritonavir, theophylline); decreased (cimetidine, amiodarone, fluoxetine, quinidine, ritonavir) and CPY1A2 (also known as cutaneovisceral angiomatosis) also presents with many vascular anomalies such as aneurysms and stroke, coarctation of the aorta, eye abnormalities. Sternal raphe defects such as pits, scars, or supraumbilical raphe are infrequently observed. Evaluation of children at risk for PHACE is important both to detect any underlying abnormalities and also before starting systemic therapy, which may be indicated given the size and location of the IH typically associated with this syndrome. PHACE children with cervical and intracranial arterial abnormalities are at increased risk of cerebrovascular accidents and specialized care by an experienced multidisciplinary team is essential.

**Multifocal Infantile Hemangioma**

Diffuse neonatal hemangiomatosis (or benign neonatal hemangiomatosis) is a historical term to describe a condition in which numerous or multifocal vascular lesions are widely distributed (Fig. 650-9). In the past, several distinct diagnoses have been lumped together under this clinical phenotype with mortality cited as high as 60-80%. Upon further analysis, this group of disorders has been found to comprise several distinct entities which are important to distinguish from one another given their varying prognoses and management strategies. Multifocal IHs may occur in the skin as well as visceral organs, but remain GLUT-1–positive when biopsied, have a relatively good prognosis with low morbidity, and respond to systemic propranolol just as solitary cutaneous IH. **Multifocal lymphangioendotheliomatosis** (also known as cutaneovisceral angiomatosis) also presents with many vascular tumors in the skin and visceral organs, but is GLUT-1–negative and complicated by severe thrombocytopenia and gastrointestinal bleeding with high mortality. Therefore accurate diagnosis in patients who present with multifocal vascular tumors is critical so early, appropriate management may be initiated.
Kaposiform Hemangioendothelioma
Kaposiform hemangioendothelioma (KHE) is a rare and potentially life-threatening vascular tumor. Initial cases described IHs with purpura and coagulopathy, but these are now known to have been KHE. KHE classically present as a red to purple firm plaque on the lateral neck, axilla, trunk or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. Tufted angiomma, once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 650-10). The main complication of these tumors is the development of Kasabach-Merritt phenomenon (KMP), which may be fatal; therefore, early diagnosis and treatment is important. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

Kasabach-Merritt Phenomenon
KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. The platelet count is depressed, but the bone marrow contains increased numbers of normal or immature megakaryocytes. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 484.6).

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. Ongoing studies of sirolimus use in KHE patients are underway; initial case reports have been promising. The mortality rate overall once patients have KMP is significant.

Pyogenic Granuloma (Lobular Capillary Hemangioma)
A pyogenic granuloma (PG) is a small red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (Fig. 650-11). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauteryization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with pulsed-dye laser therapy.

Angiokeratoma of Mibelli
Angiokeratoma of Mibelli is characterized by 1-8 mm red, purple, or black scaly, verrucose, occasionally crusted papules and nodules that appear on the dorsum of the fingers and toes and on the knees and the elbows. Less commonly, palms, soles, and ears may be affected. In many patients, onset has followed frostbite or chilblains. These nodules bleed freely after injury and may involute in response to trauma. They may be effectively eradicated by cryotherapy, electrofulguration, excision, or laser ablation.

Spider Angioma
A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (Fig. 650-12). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region,
lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.

**Maffucci Syndrome**

The association of spindle cell hemangiomas with nodular enchondromas in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as Maffucci syndrome. Maffucci syndrome is caused by somatic mosaic mutations in the IDH1 and IDH2 genes. Vascular lesions are typically soft, compressible, asymptomatic blue to purple subcutaneous masses that grow in proportion to a child’s growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 501).

**Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)**

Hereditary hemorrhagic telangiectasia (HHT), which is inherited as an autosomal dominant trait, occurs in 2 types. The gene in HHT-1 encodes endoglin (ENG), a membrane glycoprotein on endothelial cells that binds transforming growth factor-β. HHT-2 is caused by mutations in the ACVRL1 gene (activin A receptor type 2-like kinase 1) and is associated with increased risk for hepatic involvement and pulmonary hypertension. Affected children may experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions. The mucocutaneous lesions, which usually develop at puberty, are 1-4 mm, sharply demarcated red to purple macules, papules, or spider-like projections, each composed of a tightly woven mat of tortuous telangiectatic vessels (Fig. 650-13). The nasal mucosa, lips, and tongue are usually involved; less commonly, cutaneous lesions occur on the face, ears, palms, and nail beds. Vascular ectasias may also arise in the conjunctivae, larynx, pharynx, gastrointestinal tract, bladder, vagina, bronchi, brain, and liver.

Massive hemorrhage is the most serious complication of HHT and may result in severe anemia. Bleeding may occur from the nose, mouth, gastrointestinal tract, genitourinary tract, or lungs; epistaxis is often the only complaint occurring in 80% of patients. Approximately 15-20% of patients with AVMs in the lungs present with stroke due to embolic abscesses (Fig. 650-14). Persons with HHT have normal levels of clotting factors and an intact clotting mechanism. In the absence of serious complications, the life span of a person with HHT is normal. Local lesions may be ablated temporarily with chemical cautery or electrocoagulation. More drastic surgical measures may be required for lesions in critical sites, such as the lung or gastrointestinal tract. Bevacizumab, an antiangiogenic endothelial growth factor agent, has been effective in treating affected patients with HHT, who have high cardiac output secondary to hepatic AVMs.

**Ataxia-Telangiectasia**

See Chapter 597.1.

Ataxia-telangiectasia is transmitted as an autosomal recessive trait because of a mutation in the ATM gene. The characteristic telangiectasias develop at approximately 3 yr of age, first on the bulbar conjunctiva and later on the nasal bridge, malar areas, external ears, hard palate, upper anterior chest, and antecubital and popliteal fossae. Additional cutaneous stigmata include café-au-lait spots, premature graying of the hair, and sclerodermatous changes. Progressive cerebellar ataxia, neurologic deterioration, sinopulmonary infections, and malignancies are also seen.

**Angiokeratoma Corporis Diffusum (Fabry Disease)**

See Chapter 86.4.

An inborn error of glycolipid metabolism (α-galactosidase), angiokeratoma corporis diffusum is an X-linked recessive disorder that is fully penetrant in males and is of variable penetrance in carrier females. Angiokeratomas appear before puberty and occur in profusion over the genitalia, hips, buttocks, and thighs and in the umbilical and inguinal regions. They consist of 0.1-3.0 mm red to blue-black papules that may have a hyperkeratotic surface. Telangiectasias are seen in the mucosa and conjunctiva. On light microscopy, these angiokeratomas appear as blood-filled, dilated, endothelium-lined vascular spaces. Granular lipid deposits are demonstrable in dermal macrophages, fibrocytes, and endothelial cells.

Additional clinical manifestations include recurrent episodes of fever and agonizing pain, cyanosis and flushing of the acral limb areas, parasthesias of the hands and feet, corneal opacities detectable on slit-lamp examination, and hypohidrosis. Renal involvement and cardiac involvement are the usual causes of death. The biochemical defect is a deficiency of the lysosomal enzyme α-galactosidase, with accumulation of ceramide trihexoside in tissues, particularly vascular endothelium, and excretion in urine (see Chapter 86.4 for therapy). Similar cutaneous lesions have also been described in another lysosomal enzyme disorder, α-L-fucosidase deficiency, and in sialidosis, a storage disease with neuraminidase deficiency.

*Bibliography is available at Expert Consult.*

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**Figure 650-13** Hereditary hemorrhagic telangiectasia. Telangiectasias are found on the lips, oral mucosa, nasal mucosa, skin, and conjunctiva. Epistaxis is the most common manifestation of the disease. Blood transfusions may be required. (From Habif TP: Clinical dermatology: a color guide to diagnosis and therapy, ed 4, Philadelphia, 2004, Mosby, Fig. 23-22, p. 831.)

Nevus skin lesions are characterized histopathologically by collections of well-differentiated cell types normally found in the skin. Vascular nevi are described in Chapter 650. Melanocytic nevi are subdivided into 2 broad categories: those that appear after birth (acquired nevi) and those that are present at birth (congenital nevi).

**ACQUIRED MELANOCYTIC NEVUS**

Melanocytic nevus is a benign cluster of melanocytic nevus cells that arises as a result of alteration and proliferation of melanocytes at the epidermal–dermal junction.

**Epidemiology**

The number of acquired melanocytic nevi increases gradually during childhood and more slowly in early adulthood. The number reaches a plateau in the 3rd or 4th decade and then slowly decreases thereafter. The mean number of melanocytic nevi in an adult varies depending on genetics, skin color, and sun exposure. The greater the number of nevi present, the greater is the risk for development of melanoma, though the majority of melanomas arise de novo. Sun exposure during childhood, particularly intermittent, intense exposure of an individual with light skin, and a propensity to burn and freckle rather than tan are important determinants of the number of melanocytic nevi that develop. Red-haired children, despite their light skin and propensity to freckle and sunburn, have fewer nevi than other children. Increased numbers of nevi are also associated with immunosuppression and administration of chemotherapy.

**Clinical Manifestations**

Nevocellular nevi have a well-defined life history and are classified as **junctional, compound, or dermal** in accordance with the location of the nevus cells in the skin. In childhood, >90% of nevi are junctional; melanocyte proliferation occurs at the junction of the epidermis and dermis to form nests of cells. Junctional nevi appear anywhere on the body in various shades of brown; they are relatively small, discrete, flat, and variable in shape. The melanized nevus cells are cuboidal or epithelioid in configuration and occur in nests on the epidermal side of the basement membrane. Although some nevi, particularly those on the palms, soles, and genitalia, remain junctional throughout life, most become compound as melanocytes migrate into the papillary dermis to form nests at both the epidermal–dermal junction and within the dermis. If the junctional melanocytes stop proliferating, nests of melanocytes remain only within the dermis, forming an intradermal nevus. With maturation, compound and intradermal nevi may become raised, dome-shaped, verrucous, or pedunculated. Slightly elevated lesions are usually compound. Distinctly elevated lesions are usually intradermal. With age, the dermal melanocytic nests regress and the nevi gradually disappear.

**Prognosis and Treatment**

Acquired pigmented nevi are benign, but a very small percentage undergo malignant transformation. Suspicious changes are indications for excision and histopathologic evaluation; they include rapid increase in size; development of satellite lesions; variegation of color; particularly with shades of red, brown, gray, black, and blue; pigmentedary incontinence; notching or irregularity of the borders; changes in texture such as scaling, erosion, ulceration, and induration; and regional lymphadenopathy. Most of these changes are from irritation, infection, or maturation; darkening and gradual increase in size and elevation normally occur during adolescence and should not be cause for concern. Two common benign changes are clonal nevi (fried-egg moles) and eclipse nevi. A clonal nevus is light brown with a dark raised center representing a clonal change of a subset of nevus cells within the lesion. Eclipse nevi are flat and light brown with dark brown rims. They are seen primarily in the scalp (Fig. 651-1). Consideration should be given to the presence of risk factors for development of melanoma and the patient’s parents’ wishes about removal of the nevus. If doubt remains about the benign nature of a nevus, excision is a safe and simple outpatient procedure that may be justified to allay anxiety.

**ATYPICAL MELANOCYTIC NEVUS**

Atypical melanocytic nevi occur both in an autosomal dominant familial melanoma-prone setting (familial mole–melanoma syndrome, dysplastic nevus syndrome, BK mole syndrome) and as a sporadic event. Only 2% of all pediatric melanomas occur in individuals with this familial syndrome; melanoma develops before age 20 yr in 10% of individuals with the syndrome. Malignant melanoma has been reported in children with the dysplastic nevus syndrome as young as 10 yr. Risk for development of melanoma is essentially 100% in individuals with dysplastic nevus syndrome who have 2 family members who have had melanomas. The term atypical mole syndrome describes lesions in those individuals without an autosomal dominant familial history of melanoma but with more than 50 nevi, some of which are atypical. The lifetime risk of melanoma associated with dysplastic nevi in this context is estimated to be 5-10%.

Atypical nevi tend to be large (5-15 mm) and round to oval. They have irregular margins and variegated color, and portions of them are elevated. These nevi are most common on the posterior trunk, suggesting that intermittent, intense sun exposure has a role in their genesis. They may also occur in sun-protected areas such as the breasts, buttocks, and scalp. Atypical nevi do not usually develop until puberty, although scalp lesions may be present earlier. Atypical nevi demonstrate disordered proliferation of atypical intraepidermal melanocytes, lymphocytic infiltration, fibroplasia, and angiogenesis. It may be helpful to obtain histopathologic documentation of dysplastic change by biopsy to identify these individuals. It is prudent to excise borderline atypical nevi in immunocompromised children or in those treated with irradiation or chemotherapeutic agents. Although chemotherapy is associated with the development of a greater number of melanocytic nevi, it has not been directly linked to increased risk for development of melanoma. The threshold for removal of clinically atypical nevi is also lower at sites that are difficult to observe, such as the scalp. Children with atypical nevi should undergo a complete skin examination every 6-12 mo. In these children, photographic mole mapping serves as a useful adjunct in following nevus change. Parents must be counseled about the importance of sun protection and avoidance and should be instructed to look for early signs of melanoma on a regular basis, approximately every 3-4 mo.
**CONGENITAL MELANOCYTIC NEVUS**

Congenital melanocytic nevi are present in ~1% of newborn infants. These nevi have been categorized by size: giant congenital nevi are >20 cm in diameter (adult size) or >5% of the body surface; small congenital nevi are <1.5 cm in diameter, and intermediate nevi are in between these dimensions. Congenital nevi are characterized by the presence of nevus cells in the lower reticular dermis; between collagen bundles; surrounding cutaneous appendages, nerves, and vessels in the lower dermis; and occasionally extending to the subcuticular fat. They often harbor NRAS mutations, but not BRAF mutations typically seen in regular melanocytic nevi. Identification is often uncertain, however, because they may have the histologic features of ordinary junctional, compound, or intradermal nevi. Some nevi that were not present at birth display histopathologic features of congenital nevi; these should not be considered congenital. Furthermore, congenital nevi may be difficult to distinguish clinically from other types of pigmented lesions, adding to the difficulty that parents may have in identifying nevi that were present at birth. The clinical differential diagnosis includes dermal melanocytosis, café-au-lait macules, and smooth muscle hamartoma.

Sites of predilection for small congenital nevi are the lower trunk, upper back, shoulders, chest, and proximal limbs. The lesions may be flat, elevated, verrucous, or nodular and may be various shades of brown, blue, or black. Given the difficulty in identifying small congenital nevi with certainty, data regarding their malignant potential are controversial and likely overstated. The true incidence of melanoma in congenital nevi, especially small and medium-sized lesions, is unknown. Removal of all small congenital nevi is not warranted because the development of melanoma in a small congenital nevus is an exceedingly rare event before puberty. A number of factors must be weighed in the decision about whether or not to remove a nevus, including its location, the ability to monitor it clinically, the potential for scarring, the presence of other risk factors for melanoma, and the presence of atypical clinical features.

**Giant congenital pigmented nevi** (<1 in 20,000 births) occur most commonly on the posterior trunk (Fig. 651-2) but may also appear on the head or extremities. These nevi are of special significance because of their association with leptomeningeal melanocytosis (neurocutaneous melanocytosis) and their predisposition for development of malignant melanoma. Leptomeningeal involvement occurs most often when the nevus is located on the head or midline on the trunk, particularly when associated with multiple “satellite” melanocytic nevi (>20 lesions). Nevus cells within the leptomeninges and brain parenchyma may cause increased intracranial pressure, hydrocephalus, seizures, intellectual disability, and motor deficits and may result in melanoma. Malignancy can be identified by careful cytologic examination of the cerebrospinal fluid for melanin-containing cells. MRI demonstrates asymptomatic leptomeningeal melanosis in ~30% of individuals with giant congenital nevus of the type described above. The overall incidence of malignant melanoma arising in a giant congenital nevus has been estimated to be ~5-10% but is more likely to be approximately 1-2%. The median age at diagnosis of the melanomas that arise within a giant congenital nevus is 7 yr. The mortality rate approaches 100%. The risk of melanoma is greater in patients in whom the predicted adult size of the nevus is >40 cm, lesions on trunk, and presence of satellite lesions. Management of giant congenital nevus remains controversial and should involve the parents, pediatrician, dermatologist, and plastic surgeon. If the nevus lies over the head or spine, MRI may allow detection of neural melanosis, the presence of which makes gross removal of a nevus from the skin a futile effort. In the absence of neural melanosis, early excision and repair aided by tissue expanders or grafting may reduce the burden of nevus cells and thus the potential for development of melanoma, but at the cost of many potentially disfiguring operations. Nevus cells deep within subcutaneous tissues may evade excision. Random biopsies of the nevus are not helpful, but biopsy of newly expanding nodules is indicated. Follow-up every 6 mo for 5 yr and every 12 mo thereafter is recommended. Serial photographs of the nevus may aid in detecting changes.

**MELANOMA**

Malignant melanoma accounts for 1-3% of all pediatric malignancies, and approximately 2% of all melanomas occur before age 20 yr. The incidence of melanoma continues to increase. Melanoma is 7 times more frequent in the 2nd decade of life than in the 1st decade of life. Melanoma develops primarily in white individuals, on the head and trunk in males, and on the extremities in females. Risk factors for development of melanoma include the presence of the familial atypical mole–melanoma syndrome or xeroderma pigmentosum; an increased number of acquired melanocytic nevi, or atypical nevi; fair complexion; excessive sun exposure, especially intermittent exposure to intense sunlight; a personal or family (1st-degree relative) history of a previous melanoma, giant congenital nevus, and immunosuppression. In previously well children, UV radiation is responsible for most melanomas. Fewer than 5% of childhood melanomas develop within giant congenital nevi or in individuals with the familial atypical mole–melanoma syndrome. Approximately 40-50% of the time, melanoma develops at a site where there was no apparent nevus. The mortality rate from melanoma is related primarily to tumor thickness and the level of invasion into the skin. The overall mortality rate reaches ~40%, regardless of whether the tumor arises in a child or adult.

Given the lack of effective therapy for melanoma, prevention and early detection are the most effective measures. Emphasis should be given to avoidance of intense midday sun exposure between 10 AM and 3 PM; wearing of protective clothing such as a hat, long sleeves, and pants; and use of sunscreen. Early detection includes frequent clinical and photographic examinations of patients at risk (dysplastic nevus syndrome) and prompt response to rapid changes in nevi (size, shape, color, inflammation, bleeding or crusting, and sensation). The ABCD rule (asymmetry, border irregularities, color variability, diameter >6 mm), which is a useful screening tool for adults, may not be as effective for children.

**HALO NEVUS**

Halo nevi occur primarily in children and young adults, most commonly on the back (Fig. 651-3). Development of the lesion may coincide with puberty or pregnancy. Several pigmented nevi frequently develop halos simultaneously. Subsequent disappearance of the central nevus over several months is the usual outcome, and the depigmented area usually repigments. Excision and histopathologic examination of the lesion is indicated only when the nature of the central lesion is in question. An acquired melanocytic nevus occasionally develops a peripheral zone of depigmentation over a period of days to weeks. There is a dense inflammatory infiltrate of lymphocytes and histiocytes in addition to the nevus cells. The pale halo reflects disappearance of the melanocytes. This phenomenon is associated with congenital nevi.

*Figure 651-2* “Bathing suit” large congenital melanocytic nevus.
ZOSTERIFORM LENTIGINOUS NEVUS (AGMINATED LENTIGINES)
Zosteriform lentiginous nevus is a unilateral, linear, band-like collection of numerous 2-10 mm brown or black macules on the face, trunk, or limbs. The nevus may be present at birth or may develop during childhood. There are higher numbers of melanocytes in elongated rete ridges of the epidermis.

NEVUS SPILUS (SPECKLED LENTIGINOUS NEVUS)
Nevus spilus is a flat brown patch within which are darker flat or raised brown melanocytic elements (Fig. 651-5). It varies considerably in size and can occur anywhere on the body. The color of the macular component may vary from light to dark brown, and the number of darker lesions may be low or high. Nevus spilus is rare at birth and is commonly acquired in late infancy or early childhood. Dark elements within the nevus are usually present initially and tend to increase in number gradually over time. The darker macules represent nevus cells in a junctional or dermal location; the patch has increased numbers of melanocytes in a lentiginous epidermal pattern. The malignant potential of these nevi is uncertain; nevus spilus is found more commonly in individuals with melanoma than in matched control subjects. The nevi need not be excised, unless atypical features or recent clinical changes are noted.

NEVUS OF OTA AND NEVUS OF ITO
Nevus of Ota is more common among females and Asian, and African-American patients. This nevus consists of a permanent patch composed of partially confluent blue, black, and brown macules. Enlargement and darkening may occur with time. Occasionally, some areas of the nevus are raised. The macular nevi resemble the more common dermal melanocytosis of the lower back and buttocks in color and occur unilaterally in the areas supplied by the 1st and 2nd divisions of the trigeminal nerve. Nevus of Ota differs from a more common dermal melanocytosis patch, not only by its distribution but also by having a speckled rather than a uniform appearance. Both are forms of mid-dermal melanocytosis. Nevus of Ota also has a greater concentration of elongated, dendritic dermal melanocytes located in the upper rather than the lower portion of the dermis. This nevus is sometimes present at birth; in other cases, it may arise during the 1st or 2nd decade of life. Patchy involvement of the conjunctiva, hard palate, pharynx, nasal mucosa, buccal mucosa, or tympanic membrane occurs in some patients. Malignant change is exceedingly rare. Laser therapy may effectively decrease the pigmentation but can be unpredictable.

NEVUS OF ITO
Nevus of Ito is localized to the supraclavicular, scapular, and deltoid regions. This nevus tends to be more diffuse in its distribution and less mottled than nevus of Ota. It is also a form of mid-dermal blue nevi, Spitz nevi, dysplastic nevi, neurofibromas, and primary and secondary malignant melanoma, and occasionally with poliosis, Vogt-Koyanagi-Harada syndrome, and pernicious anemia. Patients with vitiligo have an increased incidence of halo nevi. Individuals with halo nevi have circulating antibodies against the cytoplasm of melanocytes and nevus cells.

SPITZ NEVUS (SPINDLE AND EPITHELIOID CELL NEVUS)
Spitz nevus manifests most commonly in the 1st 2 decades of life as a pink to red, smooth, dome-shaped, firm, hairless papule on the face, shoulder, or upper limb (Fig. 651-4). Most are <1 cm in diameter, but they can achieve a size of 3 cm. Rarely, they occur as numerous grouped lesions. Visually similar lesions include pyogenic granuloma, hemangioma, nevocellular nevus, juvenile xanthogranuloma, and basal cell carcinoma, but these entities are histologically distinguishable. Spitz nevus may be difficult to distinguish histopathologically from malignant melanoma because nuclear atypia is a common feature, particularly after local recurrence of the nevus. Difficulty arises in the fact that many other clinical types of melanocytic nevi have a similar histologic appearance. Local recurrence after excision may occur up to 5% of the time. If a nevus arouses clinical suspicion that it may be a melanoma, an excisional biopsy of the entire lesion is recommended. If the margins of excision of a Spitz nevus are positive, reexcision of the site is prudent to avoid difficulties in histopathologic interpretation of the lesion in the future.
melanocytosis. The only available treatments are masking with cosmetics and laser therapy.

**BLUE NEVI**
The common blue nevus is a solitary, asymptomatic, smooth, dome-shaped, blue to blue-gray papule <10 mm in diameter on the dorsal aspect of the hands and feet. Rarely, common blue nevi form large plaques. Blue nevi is nearly always acquired, often during childhood and more commonly in females. Microscopically, it is characterized by groups of intensely pigmented spindle-shaped melanocytes in the dermis. This nevus is benign.

The cellular blue nevus is typically 1-3 cm in diameter and occurs most frequently on the buttocks and in the sacrococcygeal area. In addition to collections of deeply pigmented dermal dendritic melanocytes, cellular islands composed of large spindle-shaped cells are noted in the dermis and may extend into the subcutaneous fat. A histologic continuum may be seen from blue nevus to cellular blue nevi. A combined nevus is the association of a blue nevus with an overlying melanocytic nevus.

The blue-gray that is characteristic of these nevi is an optical effect caused by dermal melanin. Longer wavelengths of visible light penetrate to the deep dermis and are absorbed there by melanin; shorter-wavelength blue light cannot penetrate deeply but instead is reflected back to the observer.

**NEVUS DEPIGMENTOSUS (ACHROMIC NEVUS)**
Nevi depigmentosi are usually present at birth; they are localized macular hypopigmented patches or streaks, often with bizarre, irregular borders (Fig. 651-6). They can resemble hypomelanosis of Ito clinically, except that they are more localized and often unilateral. Small lesions may also resemble the ash leaf macules of tuberous sclerosis. Nevus depigmentosi appear to represent a focal defect in transfer of melanosome to keratinocytes.

![Figure 651-6 Large nevus depigmentosus of the abdomen.](image)

**NEVUS SEBACEOUS (JADASSOHN)**
A relatively small, sharply demarcated, oval or linear, elevated yellow-orange plaque that is usually devoid of hair, nevus sebaceus occurs on the head and neck of infants (Fig. 651-8). Although the lesion is characterized histopathologically by an abundance of sebaceous glands, all
Cutaneous Nevii

NEVUS COMEDONICUS
An uncommon organoid nevus of epithelial origin, nevus comedonicus consists of linear plaques of plugged follicles that simulate comedones; they may be present at birth or may appear during childhood. The horny plugs represent keratinous debris within dilated, malformed pilosebaceous follicles. The lesions are most often unilateral and may develop at any site. Rarely, they are associated with other congenital malformations, including skeletal defects, cerebral anomalies, and cataracts. Although these lesions are often asymptomatic, some affected individuals experience recurrent inflammation, resulting in cyst formation, fistulas, and scarring. There is no effective treatment except full-thickness excision; palliation of larger lesions may be achieved by regular applications of a retinoic acid preparation.

CONNECTIVE TISSUE NEVUS
Connective tissue nevus is a hamartoma of collagen, elastin, and/or glycosaminoglycans of the dermal extracellular matrix. It may occur as a solitary defect or as a manifestation of an associated disorder. These nevi may occur at any site but are most common on the back, buttocks, arms, and thighs. They are skin-colored, ivory, or yellow plaques, 2-15 cm in diameter, composed of many tiny papules or grouped nodules that are frequently difficult to appreciate visually because of the subtle color changes. The plaques have a rubbery or cobblestone consistency on palpation. Biopsy findings are variable and include increased amounts and/or degeneration or fragmentation of dermal collagen, elastic tissue, or ground substance. Similar lesions occurring with tuberous sclerosis are called shagreen patches; however, shagreen patches consist only of excessive amounts of collagen. The association of many small papular connective tissue nevi with osteopoikilosis is called dermatofibrosis lenticularis disseminata (Buschke-Ollendorf syndrome).

SMOOTH MUSCLE HAMARTOMA
Smooth muscle hamartoma is a developmental anomaly resulting from hyperplasia of the smooth muscle (arrector pili) associated with hair follicles. It is usually evident at birth or shortly thereafter as a flesh-colored or lightly pigmented plaque with overlying hypertrichosis on the trunk or limbs (Fig. 651-10). Transient elevation or a rippling movement of the lesion, caused by contraction of the muscle bundles, can sometimes be elicited by stroking of the surface (pseudo-Darier sign). Smooth muscle hamartoma can be mistaken for congenital pigmented nevus, but the distinction is important because the former has no risk for malignant melanoma and need not be removed.
Bibliography


Hyperpigmented Lesions
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Chapter 652

DISORDERS OF PIGMENT
Normal pigmentation requires migration of melanoblasts from the neural crest to the dermal–epidermal junction, enzymatic processes to form pigment, structural components to contain the pigment (melanosomes), and transfer of pigment to the surrounding keratinocytes. Increased skin color may be generalized or localized and may result from various defects in any of these requirements. Some of these aberrations are a manifestation of systemic disease, others represent generalized or focal developmental or genetic defects, and still others may be nonspecific and the result of cutaneous inflammation.

EPHELIDES (FRECKLES)
Ephelides are light or dark brown, round, oval or irregularly shaped, well-demarcated, macules usually <3 mm in diameter that occur in sun-exposed areas such as the face, upper back, arms, and hands. They are induced by exposure to sun, particularly during the summer, and may fade or disappear during the winter. They are a result of increased sun-induced melanogenesis and melanosome transport from melanocytes to keratinocytes, and not increased number of melanocytes. They are more common in redheads and fair-haired individuals and first appear in the preschool years. Histologically, they are marked by increased melanin pigment in epidermal basal cells, which have more numerous and larger dendritic processes than the melanocytes of the surrounding paler skin. The lack of melanocytic proliferation or elongation of epidermal rete ridges distinguishes them from lentigines. Freckles have been identified as a marker for increased risk for UV-induced neoplasia and hence melanoma, independent of melanocytic nevi.

LENTIGINES
Lentigines, often mistaken for freckles or junctional nevi, are small (<3 cm), round, dark brown macules that can appear anywhere on the body with an early age of onset. They are more common in darkly pigmented than in lightly pigmented individuals. They are unrelated to sun exposure and remain permanently. Histologically, they have elongated, club-shaped, epidermal rete ridges with increased numbers of melanocytes and dense epidermal deposits of melanin. No nests of melanocytes are found. The lesions are benign and, when few, may be viewed as a normal occurrence and are seen most commonly on the lower lip.

Eruptive/generalized lentiginosis (lentiginosis profusa) involves innumerable small, pigmented macules that are present at birth or appear during childhood. There are no associated abnormalities, and mucous membranes are spared. Carney complex is an autosomal dominant syndrome characterized by multiple lentigines and multiple neoplasias, including: myxomas of the skin, heart (atrial) and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosa; growth hormone-producing pituitary adenomas; and testicular Sertoli cell tumors. Components of the Carney complex have been described previously as the NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides) and LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) syndromes. It is inherited in an autosomal dominant pattern and caused by an inactivating mutation of the PRKAR1 gene.

The multiple lentigines syndrome (formerly LEOPARD) is an autosomal dominant entity consisting of a generalized, symmetric distribution of lentigines (Fig. 652-1) in association with electrocardiogram abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitals [cryptorchidism, hypogonadism, hypospadias], growth retardation, and sensorineural deafness syndrome.

Figure 652-1 Multiple lentigines in LEOPARD (lentigines in association with electrocardiogram abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitals [cryptorchidism, hypogonadism, hypospadias], growth retardation, and sensorineural deafness) syndrome.

Café-au-lait spots vary tremendously in size and may be large, covering a significant portion of the trunk or limb. Generally the borders are smooth, but some have exceedingly irregular borders. The lesions are characterized by increased numbers of melanocytes and
melanin in the epidermis but lack the clubbed rete ridges that typify lentigines. One to 3 café-au-lait spots are common in normal children; ≈10% of normal children have café-au-lait macules. The spots may be present at birth or may develop during childhood.

Large, often asymmetric café-au-lait spots with irregular borders are characteristic of patients with Albright (McCune-Albright) syndrome (GNAS1 gene; see Chapter 562.6). This disorder includes polyostotic fibrous dysplasia of bone, leading to pathologic fractures; precocious puberty; and numerous hyperfunctional endocrinopathies. The macular hyperpigmentation may be present at birth or may develop later in childhood (see Fig. 652-3). Cutaneous pigmentation is typically most extensive on the side showing the most severe bone involvement.

**Neurofibromatosis Type 1 (von Recklinghausen Disease)**

The café-au-lait spot (macule) is the most familiar cutaneous hallmark of the autosomal dominant neurocutaneous syndrome known as neurofibromatosis type 1 (NF-1, neurofibromin gene; see Fig. 652-2 and Chapter 596.1). Included in the criteria for this diagnosis is the presence of 5 or more café-au-lait spots >5 mm in diameter in prepubertal patients or 6 or more café-au-lait spots >15 mm in diameter in postpubertal patients. Multiple café-au-lait macules commonly produce a freckled appearance of non–sun-exposed areas such as the axillae (Crowe sign), the inguinal and inframammary regions, and under the chin. Café-au-lait macules can also be seen in segmental NF-1 which results from somatic mosaicism arising from postzygotic mutations in the NF-1 gene such that the clinical manifestations of NF-1 are present only in a localized body segment. Another variant of NF-1 is hereditary spinal neurofibromatosis, which is a rare disorder that generally presents with multiple café-au-lait macules and multiple, symmetric spinal root neurofibromas but other stigmata of NF-1 are typically absent. The lesions also occur with certain other disorders, including other types of neurofibromatosis, but in these disorders the café-au-lait spots are not a major feature of the disorder (Table 652-1).

<table>
<thead>
<tr>
<th>STRENGTH OF ASSOCIATION</th>
<th>SYNDROME</th>
<th>CLINICAL FEATURES</th>
<th>GENE OR LOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Neurofibromatosis type 2</td>
<td>Acoustic neuromas, schwannomas, neurofibromas, meningiomas, juvenile posterior subcapsular lenticular opacity; café-au-lait seen but not a criterion for diagnosis</td>
<td>NF-2</td>
</tr>
<tr>
<td></td>
<td>Multiple familial café-au-lait</td>
<td>Multiple café-au-lait without other stigmata of NF-1</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Legius (NF-1-like) syndrome</td>
<td>Multiple café-au-lait and skinfold freckling without other stigmata of NF-1</td>
<td>SPRED1</td>
</tr>
<tr>
<td></td>
<td>McCune-Albright syndrome</td>
<td>Segmental café-au-lait, precocious puberty, other endocrinopathies, polyostotic fibrous dysplasia</td>
<td>GNAS1</td>
</tr>
<tr>
<td></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
<td>Multiple café-au-lait, adenomatous colonic polyps, multiple malignancies, including colonic adenocarcinoma, glioblastoma, medulloblastoma, and lymphoma</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td></td>
<td>Ring chromosome syndromes</td>
<td>Multiple café-au-lait, microcephaly, mental retardation, short stature, skeletal anomalies</td>
<td>Chromosomes 7, 11, 12, 15, 17</td>
</tr>
<tr>
<td></td>
<td>LEOPARD/multiple lentigines syndrome</td>
<td>Café-au-lait, café-noir, lentigines, cardiac conduction defects, ocular hypertelorism, pulmonary stenosis, genitourinary anomalies, growth retardation, hearing loss</td>
<td>PTPN11</td>
</tr>
<tr>
<td></td>
<td>Cowden syndrome (multiple hamartoma syndrome)</td>
<td>Facial trichilemmomas, cobblestoning of the oral mucosa, predisposition to soft tissue tumors (lipomas, neuromas), gastrointestinal polyps, fibrocystic breast disease and breast carcinoma, thyroid adenoma, and thyroid cancer</td>
<td>PTEN</td>
</tr>
</tbody>
</table>

*Figure 652-2 Multiple café-au-lait macules on a child with neurofibromatosis type 1. (From Eichenfield LF, Frieden IJ, Esterly NB: Textbook of neonatal dermatology, Philadelphia, 2001, WB Saunders, p. 372.)*
<table>
<thead>
<tr>
<th>STRENGTH OF ASSOCIATION</th>
<th>SYNDROME</th>
<th>CLINICAL FEATURES</th>
<th>GENE OR LOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Bannayan-Riley-Ruvalcaba syndrome</td>
<td>Facial trichilemmomas, oral papillomas, pigmented genital macules, gastrointestinal polyps, macrocephaly, vascular anomalies, mental retardation</td>
<td>PTEN</td>
</tr>
<tr>
<td>Weak</td>
<td>Ataxia-telangiectasia</td>
<td>Cerebellar ataxia, cutaneous and ocular telangiectasias, immunodeficiency, hypogonadism, predisposition to lymphoreticular malignancy</td>
<td>ATM</td>
</tr>
<tr>
<td></td>
<td>Bloom syndrome</td>
<td>Photosensitivity, immunodeficiency, chronic lung disease, cryptorchidism, sydactyly, short stature, susceptibility to malignancy</td>
<td>RECQL3</td>
</tr>
<tr>
<td></td>
<td>Fanconi anemia</td>
<td>Bone marrow failure, multiple congenital anomalies, predisposition to malignancy, mental retardation, microcephaly</td>
<td>FANCA, FANCB (putative), FANCC, FANCD locus on chromosome 3, FANCE locus on chromosome 6, FANCF, FANCG, FANCI (putative)</td>
</tr>
<tr>
<td>Strong</td>
<td>Russell-Silver syndrome</td>
<td>Short stature, craniofacial and body asymmetry, low birthweight, microcephaly, triangular facies, fifth finger clinodactyly, congenital cardiac defects</td>
<td>?</td>
</tr>
<tr>
<td>Strong</td>
<td>Tuberous sclerosis</td>
<td>Facial angiofibromas, cutaneous collagenomas, seizures, mental retardation, hypomelanotic macules, perinatal fibromas, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, pulmonary lymphangiomatosis renal angiomyolipoma, retinal hamartomas</td>
<td>TSC1, TSC2</td>
</tr>
<tr>
<td>Weak</td>
<td>Turner syndrome</td>
<td>Short stature, lymphedema, congenital heart disease, valgus deformity</td>
<td>X-chromosomal anomalies (XO karyotype or Xp deletion)</td>
</tr>
<tr>
<td>Strong</td>
<td>Noonan syndrome</td>
<td>Facial dysmorphism, pulmonary valve stenosis, webbed neck, pectus excavatum, mental retardation, short stature, cryptorchidism, hematologic malignancies</td>
<td>PTPN11, SOS1, RAF1, KRAS</td>
</tr>
<tr>
<td>Strong</td>
<td>Multiple mucosal neuroma (MEN) syndrome 1</td>
<td>Parathyroid adenoma, pituitary adenoma, pancreatic islet adenoma, lipoma, gingival papules, facial angiofibromas, collagenomas</td>
<td>MENIN</td>
</tr>
<tr>
<td>Strong</td>
<td>MEN syndrome 2B</td>
<td>Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma, parathyroid adenoma, marfanoid habitus</td>
<td>RET</td>
</tr>
<tr>
<td>Strong</td>
<td>Johanson-Blizzard syndrome</td>
<td>Short stature, failure to thrive, microcephaly, sensorineural hearing loss, dental anomalies, congenital heart disease, exocrine pancreatic insufficiency, imperforate anus, genitourinary anomalies, mental retardation, hypothyroidism</td>
<td>UBR1</td>
</tr>
<tr>
<td>Strong</td>
<td>Microcephalic osteodysplastic primordial dwarfism, type II</td>
<td>Short stature, microcephaly, intrauterine growth retardation, dysmorphic facies, skeletal anomalies, developmental delay, premature puberty</td>
<td>PCNT2</td>
</tr>
<tr>
<td>Strong</td>
<td>Nijmegen breakage syndrome</td>
<td>Short stature, growth retardation, microcephaly, cleft lip/palate, dysmorphic facies, bronchiectasis, sinusitis, dysgammaglobulinemia with recurrent urinary tract and gastrointestinal infections, mental retardation, spontaneous chromosomal instability, predisposition to malignancy</td>
<td>NBS1</td>
</tr>
<tr>
<td>Strong</td>
<td>Rubinstein-Taybi syndrome</td>
<td>Short stature, microcephaly, dysmorphic facies, congenital cardiac disease, sternal anomalies, skeletal anomalies, mental retardation</td>
<td>CREBBP, EP300</td>
</tr>
<tr>
<td>Strong</td>
<td>Kabuki syndrome</td>
<td>Postnatal growth retardation, microcephaly, dysmorphic facies, congenital hip dysplasia, hirsutism, mental retardation</td>
<td>?</td>
</tr>
</tbody>
</table>

INCONTINENTIA PIGMENTI
(BLOCH-SULZBERGER DISEASE)
See Chapter 596.7.

POSTINFLAMMATORY PIGMENTARY CHANGES
Either hyperpigmentation or hypopigmentation can occur as a result of cutaneous inflammation. Alteration in pigmentation usually follows a severe inflammatory reaction but may result from mild dermatitis. Dark-skinned children are more likely to show these changes than fair-skinned ones. Although altered pigmentation may persist for weeks to months, patients can be reassured that these lesions are usually temporary.

Bibliography is available at Expert Consult.
Bibliography
Chapter 653 ➤ Hypopigmented Lesions
Sheila S. Galbraith

**ALBINISM**

Several types of congenital oculocutaneous albinism (OCA) consist of partial or complete failure of melanin production in the skin, hair, and eyes despite the presence of normal number, structure, and distribution of melanocytes. They may be divided into 2 major classes: those with abnormal protein function involved in the formation and transfer of melanin, and those with defects in melanosomes (Table 653-1).

Tyrosinase is the copper-containing enzyme that catalyzes at multiple steps in melanin biosynthesis (see Chapter 85.2). Tyrosinase-positive variants are characterized by darkening of the hair bulb on incubation with tyrosine.

**Oculocutaneous albinism type 1 (OCA1)** is characterized by great reduction in or absence of tyrosinase activity. OCA1A, the most severe form, is characterized by a lack of visible pigment in hair, skin, and eyes (Fig. 653-1). This manifests as photophobia, nystagmus, defective visual acuity, white hair, and white skin. The irises are blue-gray in oblique light and prominent pink in reflected light. OCA1B, or yellow mutant albinism, manifests at birth as white hair, pink skin, and gray eyes. This type is particularly prevalent in Amish communities. Progressively the hair becomes yellow-red, the skin tans lightly on exposure to the sun, and the irises may accumulate some brown pigment, with a resultant improvement in visual acuity. Photophobia and nystagmus are present but mild. OCA TS is a temperature-sensitive type of albinism. The abnormal tyrosinase has decreased activity at 35-37°C (95-98.6°F). Therefore, cooler regions of the body such as the limbs and head pigment to some degree, whereas other areas remain depigmented.

**OCA2** ranges from nearly normal to closely resembling type 1 albinism. This is the most common form of albinism seen worldwide. Little or no melanin is present at birth, but pigment, particularly red-yellow pigment, may accumulate during childhood to produce straw-colored or light brown skin in white individuals. Pigmented nevi may develop. Progressive improvement in visual acuity and nystagmus occurs with aging. Black individuals may have yellow-brown skin, dark-brown freckles in sun-exposed areas, and brown coloration of the irises. **Brown OCA** is an allelic variant of OCA2. Prader-Willi and Angelman syndromes, which include hypopigmentation, have deletions that include the gene involved in OCA2.

**OCA3** (rufous albinism) is seen predominantly in patients of African descent. It is characterized by red hair, reddish brown skin, pigmented nevi, freckles, reddish brown to brown eyes, nystagmus, photophobia, and decreased visual acuity.

### Table 653-1 | Genes Associated with Hypopigmentation

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>GENE DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OCULOCUTANEOUS ALBINISM</strong></td>
<td></td>
</tr>
<tr>
<td>OCA1</td>
<td>Tyrosinase</td>
</tr>
<tr>
<td>OCA2</td>
<td>P protein</td>
</tr>
<tr>
<td>OCA3</td>
<td>TRP-1</td>
</tr>
<tr>
<td>OCA4</td>
<td>MATP</td>
</tr>
<tr>
<td><strong>HERMANSKY-PUDLAK</strong></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>HPS-1 Mouse (pale ear)</td>
</tr>
<tr>
<td>Type 2</td>
<td>HPS-2 b3A subunit of AP3</td>
</tr>
<tr>
<td>Type 3</td>
<td>HPS-3 Mouse (cocoa)</td>
</tr>
<tr>
<td>Type 4</td>
<td>HPS-4 Mouse (light ear)</td>
</tr>
<tr>
<td>Type 5</td>
<td>HPS-5 KIAA107</td>
</tr>
<tr>
<td>Type 6</td>
<td>HPS-6 Mouse (ruby eye)</td>
</tr>
<tr>
<td>Type 7</td>
<td>HPS-7 DTNBP1</td>
</tr>
<tr>
<td>Type 8</td>
<td>HPS-8 Bloc153</td>
</tr>
<tr>
<td><strong>CHÉDIAK-HIGASHI</strong></td>
<td>C5H1/LYST</td>
</tr>
<tr>
<td><strong>PIEBAULDISM</strong></td>
<td>C-KIT receptor</td>
</tr>
<tr>
<td></td>
<td>Heterozygous SLUG</td>
</tr>
<tr>
<td><strong>WAARDENBURG</strong></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Heterozygous PAX-3</td>
</tr>
<tr>
<td>Type 2a</td>
<td>MITF</td>
</tr>
<tr>
<td>Type 2b</td>
<td>Chromosome 1p</td>
</tr>
<tr>
<td>Type 2c</td>
<td>Chromosome 8p23</td>
</tr>
<tr>
<td>Type 2d</td>
<td>SNAIL</td>
</tr>
<tr>
<td>Type 3</td>
<td>Homozygous PAX-3</td>
</tr>
<tr>
<td>Type 4</td>
<td>SOX10</td>
</tr>
<tr>
<td>Type 5</td>
<td>Endothelin 3</td>
</tr>
<tr>
<td>Type 6</td>
<td>Endothelin B receptor</td>
</tr>
<tr>
<td><strong>PIEBAULDISM</strong></td>
<td></td>
</tr>
</tbody>
</table>

Tyrosinase is the copper-containing enzyme that catalyzes at multiple steps in melanin biosynthesis (see Chapter 85.2). Tyrosinase-positive variants are characterized by darkening of the hair bulb on incubation with tyrosine.
The skin ventral trunk, elbows, and knees. Islands of normal or darker-than-normal pigmentation may be present within the amelanotic areas (Fig. 653-2). The plaques are a result of a permanent localized absence of melanocytes as a result of a defect in the KIT protooncogene, which encodes the cell surface receptor transmembrane tyrosine kinase. The pattern of depigmentation arises from defective melanoblast migration from the neural crest during development. The reason that piebaldism is a localized and not a generalized process remains unknown. Piebaldism must be differentiated from vitiligo, which may be progressive and is not usually congenital, nevus depigmentosus, and Waardenburg syndrome.

**Waardenburg Syndrome**
Waardenburg syndrome also manifests at birth as localized areas of depigmented skin and hair. There are 4 types of Waardenburg syndrome. The hallmark of Waardenburg type 1 is the white forelock, which is seen in 20-60% of patients. Only 15% of patients have areas of depigmented skin. Deafness occurs in 9-37%, heterochromia irides in 20%, and unibrow (synophrys) in 17-69% of those affected. Dystopia canthorum (i.e., telecanthus) is seen in all patients with Waardenburg type 1. Waardenburg type 2 is similar to type 1, except that patients with type 2 lack dystopia canthorum, but they also have a higher incidence of deafness. Waardenburg type 3 is similar to Waardenburg type 1, except that patients also have limb abnormalities. It is also called the Klein-Waardenburg syndrome. Waardenburg type 4 is also called the Shah-Waardenburg syndrome. Patients with this type all have Hirschsprung disease. Dystopia canthorum is seldom seen in these patients.

**Hypomelanosis of Ito**
Hypomelanosis of Ito is a rare congenital skin disorder affecting children of both sexes that can have associated defects in several organ systems. There is no evidence for genetic transmission; chromosomal mosaicism and chromosomal translocations have been reported. Hypomelanosis of Ito is currently a descriptive rather than definitive diagnosis. Blaschko or mosaic hypomelanosis is a better descriptive term.

The skin lesions of hypomelanosis of Ito are generally present at birth but may be acquired in the 1st 2 yr of life. The lesions are similar to a negative image of those present in incontinentia pigmenti, consisting of bizarre, patterned, hypopigmented macules arranged over the body surface in sharply demarcated whorls, streaks, and patches that follow the lines of Blaschko (Fig. 653-3). The palms, soles, and mucous
membranes are spared. The hypopigmentation remains unchanged throughout childhood but fades during adulthood. The degree of depigmentation varies from hypopigmented to achronic. Neither inflammatory nor vesicular lesions precede the development of the pigmented changes as in incontinentia pigmenti. The hypopigmented areas demonstrate fewer and smaller melanocytes and a decreased number of melanin granules in the basal cell layer than normal. Inflammatory cells and pigment incontinence are lacking.

The majority of patients with mosaic hypomelanosis have no associated abnormalities, but involvement of other organs systems can rarely occur. The most commonly associated abnormalities involve the nervous system, including intellectual disability (70%), seizures (40%), microcephaly (25%), and muscular hypotonia (15%). The musculoskeletal system is the second most frequently involved system, affected by scoliosis and thoracic and limb deformities. Minor ophthalmologic defects (strabismus, nystagmus) are present in 25% of patients, and 10% have cardiac defects. These frequencies are likely to be overestimated because patients with isolated skin disease often do not seek further evaluation. The differential diagnosis includes systematized nevus depigmentosus, which is a stable leukoderma not associated with systemic manifestations. Differentiation from incontinentia pigmenti, particularly the hypopigmented fourth stage, is critical for genetic counseling because incontinentia pigmenti, unlike hypomelanosis of Ito, is inherited.

**Vitiligo**

**Epidemiology and Etiology**

Vitiligo is macular depigmentation associated with the destruction of melanocytes. The disorder represents a clinical end-point resulting from a complex interaction of environmental, genetic, and immunologic factors. Autoimmune, genetic, autototoxic, and neural theories have been postulated. The prevalence is 0.5% of most populations.

There is definitely an autoimmune component to vitiligo. Eighty percent of patients with active disease have an antibody to a surface antigen on pigmented melanocytes. These antibodies appear to be cytotoxic for melanocytes. There is also a correlation between disease activity and the titer of serum antimelanocyte antibody. Melanocyte-specific CD8+ T lymphocytes are also involved in the pathogenesis of vitiligo. These antibodies and T cells recognize a variety of melanocyte enzymatic and structural proteins.

The genetic epidemiology of vitiligo is part of a broader genetically determined autoimmune and autoinflammatory diathesis. Fifteen to 20% of patients with generalized vitiligo have 1 or more affected 1st-degree relatives. In these families the genetic pattern is suggestive of polygenic, multifactorial inheritance. In the other patients, the disease occurs sporadically.

Many authorities believe that the cause of melanocyte destruction in vitiligo is an endogenous cellular abnormality. It has been suggested that melanocytes are destroyed because of the accumulation of a toxic melanin synthesis intermediate and/or lack of protection from hydrogen peroxide and other oxygen radicals. There is in vitro evidence that some of these metabolites may be lethal to melanocytes. Others believe that neurochemical factors damage melanocytes and cause depigmentation. This possibility would explain the pattern of involvement in segmental vitiligo that runs roughly along the course of a dermatome.

**Clinical Manifestations**

There are 2 subtypes of vitiligo, generalized (nonsegmental) and segmental, which probably are distinctly different diseases (Table 653-2). Generalized vitiligo (85-90% of cases) may be divided into widespread (type A) and localized (type B). Approximately 50% of all patients with vitiligo have onset before 18 yr of age, and 25% demonstrate depigmentation before age 8 yr. Most children have the generalized form, but the segmental type is more common among children than among adults. Patients with the generalized form usually present with a remarkably symmetric pattern of white macules and patches (Fig. 653-4); the margins may be somewhat hyperpigmented. The
patches tend to be acral and/or periorificial. Occasionally, almost the entire skin surface becomes depigmented.

There are several varieties of localized vitiligo. A form of localized vitiligo is the halo nevus phenomenon, whereby benign moles develop depigmented rings at the periphery. Premature graying of scalp hair (canities) has also been considered a form of localized vitiligo. In segmental vitiligo, depigmented areas are limited to a quasidermatomal distribution. This type of vitiligo has a rapid onset and progression in a localized area without the development of depigmentation in other areas.

A number of autoimmune diseases occur in patients with vitiligo, including Addison disease, Hashimoto thyroiditis, pernicious anemia, diabetes mellitus, hypoparathyroidism, and polyglandular autoimmune syndrome with selective immunoglobulin A deficiency. In addition, other diseases with possible immune defects, such as alopecia areata and morphea, have been seen in patients with vitiligo.

Vogt-Koyanagi-Harada syndrome is vitiligo associated with uveitis, dysacusia, meningoencephalitis, and depigmentation of the skin, scalp hair, eyebrows, and eyelashes. In the Alezzandrini syndrome, vitiligo is associated with tapetoretinal degeneration and deafness.

Light microscopic examination of early lesions shows mild inflammatory change. Over time, degenerative changes occur in melanocytes, leading to their complete disappearance.

The differential diagnosis of vitiligo includes other causes of widespread acquired leukoderma. The two most common problem diagnoses are tinea versicolor and postinflammatory hypopigmentation.

**Treatment**

Localized areas of vitiligo may respond to potent topical steroid, topical tacrolimus, or topical pimecrolimus. In patients with more extensive involvement, narrow-band ultraviolet light B (UVB) [UVB311] is the treatment of choice. In all forms of vitiligo, response to therapy is slow, taking many months to years. For those not interested in treatment, cover-up cosmetics may be used. All areas of vitiligo are susceptible to sun damage, and care should be taken to minimize sun exposure of affected areas. Spontaneous remission may be seen in a small percentage of cases.

*Bibliography is available at Expert Consult.*
Bibliography


Many diseases are characterized by vesiculobullous lesions; they vary considerably in cause, age of onset, and pattern. The morphology and distribution of the blister often provides a visual clue to the location of the lesion within the skin. Blisters localized to the epidermal layers are thin-walled, relatively flaccid, and easily ruptured. Subepidermal blisters are tense, thick-walled, and more durable. Biopsies of blisters can be diagnostic because the level of cleavage within the skin and associated findings, such as the nature of the inflammatory infiltrate, are characteristic for a particular disorder. Other diagnostic procedures, such as immunofluorescence and electron microscopy, can often help distinguish vesiculobullous disorders that have nearly identical histopathologic findings (Table 654-1).

### Table 654-1  Sites of Blister Formation and Diagnostic Studies for the Vesiculobullous Disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>BLISTER CLEAVAGE SITE</th>
<th>DIAGNOSTIC STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>IE</td>
<td>Zn level</td>
</tr>
<tr>
<td>Bullous impetigo</td>
<td>GL</td>
<td>Smear, culture</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>SE (junctional)</td>
<td>Direct and indirect immunofluorescence studies</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>SC</td>
<td>KOH preparation, culture</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>SE</td>
<td>Direct immunofluorescence studies</td>
</tr>
<tr>
<td>Dermatophytosis</td>
<td>IE</td>
<td>KOH preparation, culture</td>
</tr>
<tr>
<td>Dyshidrotic eczema</td>
<td>IE</td>
<td>Routine histopathology</td>
</tr>
<tr>
<td>EB—simplex</td>
<td>IE</td>
<td>Electron microscopy; immunofluorescence mapping</td>
</tr>
<tr>
<td>EB of the hands and feet</td>
<td>IE</td>
<td>Electron microscopy; immunofluorescence mapping</td>
</tr>
<tr>
<td>Junctional EB (lethalis)</td>
<td>SE (junctional)</td>
<td>Electron microscopy; immunofluorescence mapping</td>
</tr>
<tr>
<td>Recessive dystrophic EB</td>
<td>SE</td>
<td>Electron microscopy; immunofluorescence mapping</td>
</tr>
<tr>
<td>Dominant dystrophic EB</td>
<td>SE</td>
<td>Electron microscopy; immunofluorescence mapping</td>
</tr>
<tr>
<td>Epidermolytic hyperkeratosis</td>
<td>IE</td>
<td>Routine histopathology</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>SE</td>
<td>Routine histopathology</td>
</tr>
<tr>
<td>Erythema toxicum</td>
<td>SC, IE</td>
<td>Smear for eosinophils</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>IE</td>
<td>Smear for eosinophils</td>
</tr>
<tr>
<td>Insect bites</td>
<td>IE</td>
<td>Routine histopathology</td>
</tr>
<tr>
<td>Kindler syndrome</td>
<td>IE, SE</td>
<td>Electron microscopy; immunostaining</td>
</tr>
<tr>
<td>Linear immunoglobulin A dermatosis</td>
<td>SE</td>
<td>Direct immunofluorescence studies</td>
</tr>
</tbody>
</table>
ETIOLOGY
Among the numerous factors implicated in the etiology of erythema multiforme (EM), infection with herpes simplex virus (HSV) is the most common. Infection with Mycoplasma pneumoniae is implicated, particularly in children and young adults, but differentiation from Stevens-Johnson syndrome and the so-called M. pneumoniae-associated mucositis (see below) can be confusing. HSV labialis and, less commonly, HSV genitalis are implicated in 60-70% of episodes of EM and are believed to trigger nearly all episodes of recurrent EM, frequently in association with sun exposure. HSV antigens and DNA are present in skin lesions of EM but are absent in nonlesional skin. The presence of the human leukocyte antigens A33, B62, B35, DQw3 (DQB1*0301 split), and DR53 is associated with an increased risk of HSV-induced EM, particularly the recurrent form. Most patients experience a single self-limited episode of EM. Lesions of HSV-induced recurrent EM typically develop 10-14 days after onset of recurrent HSV eruptions, have a similar appearance from episode to episode, but may vary in frequency and duration in a given patient. Not all episodes of recurrent HSV evolve into EM in susceptible patients.

Drug-related EM is less common (<10% of patients) and may be associated with nonsteroidal antiinflammatory agents, including acetaminophen, sulfonamides, and other antibiotics. The differential diagnosis in drug-related EM should include toxic epidermal necrolysis and drug hypersensitivity syndrome.

CLINICAL MANIFESTATIONS
EM has numerous morphologic manifestations on the skin, varying from erythematous macules, papules, vesicles, bullae, or urticarial appearing plaques to patches of confluent erythema. The eruption appears most commonly in patients between the ages of 10 and 40 yr (with highest incidence in males in the 2nd decade) and usually is asymptomatic, although a burning sensation or pruritus may be present. The diagnosis of EM is established by finding the classic lesion: doughnut-shaped, target-like (iris or bull’s-eye) papules with an erythematous outer border, an inner pale ring, and a dusky purple to necrotic center (which sometimes blisters and erodes; Figs. 654-1 and 654-2).

EM is characterized by an abrupt, symmetric cutaneous eruption, most commonly on the extensor upper extremities; lesions are relatively sparse on the face, trunk, and legs. Lesions can be seen on the palms and soles. The eruption often appears initially as red macules or urticarial plaques that expand centrifugally to form lesions up to 2 cm in diameter with a dusky to necrotic center. Lesions of a particular episode typically appear within 72 hr and remain fixed in place (average duration: 7 days). Oral lesions may occur with a predilection for the vermilion border of the lips and the buccal mucosa, but other mucosal surfaces are spared. EM may manifest initially as urticarial-like lesions, but in distinction to urticaria, a given lesion of EM does not fade within 24 hr. Prodromal symptoms are generally absent. Prognosis is favorable with limited long-term morbidity. Lesions typically resolve without sequelae in approximately 2 wk, but in darker pigmented individuals, pigmentary alterations at the site of lesions can be longstanding. Progression to Stevens-Johnson syndrome does not occur. Many authors distinguish between EM minor (mainly cutaneous typical or atypical targetoid lesions affecting less than 10% body surface area plus no or limited mucosal involvement, often limited to 1 site,
such as the mouth) from EM major (same cutaneous involvement pattern as EM minor plus 2 or more mucosal sites with more-severe oral involvement). EM major and Stevens-Johnson syndrome are accepted to be separate entities.

Pathogenesis
The pathogenesis of EM is unclear, but it may be a host-specific, cell-mediated immune response to an antigenic stimulus, resulting in damage to keratinocytes. HSV Pol1 gene expressed in HSV-induced recurrent EM lesions upregulates/activates the transcription factor SP1 and inflammatory cytokines. These cytokines, released by activated mononuclear cells and keratinocytes, may contribute to epidermal cell death and constitutional symptoms.

Pathology
Microscopic findings in EM are variable but may aid in diagnosis. Early lesions typically show slight intercellular edema, rare dyskeratotic keratinocytes, and basal vacuolation in the epidermis and a perivascular lymphohistiocytic infiltrate with edema in the upper dermis. More mature lesions show an accentuation of these characteristics and the development of lymphocytic exocytosis and an intense, perivascular, and interstitial mononuclear infiltrate in the upper third of the dermis. In severe cases, the entire epidermis becomes necrotic.

Differential Diagnosis
The differential diagnosis of EM also includes bullous pemphigoid, pemphigus, linear immunoglobulin (Ig) A dermatosis, graft-versus-host disease, fixed-drug eruption, bullous-drug eruption, urticaria, viral infections such as HSV, reactive arthritis syndromes, Kawasaki disease, Sweet syndrome, Behçet disease, allergic vasculitis, erythema annulare centrifugum, polymorphous-drug eruption, and periarteritis nodosa. EM that primarily involves the oral mucosa may be confused with Stevens-Johnson syndrome, bullous pemphigoid, pemphigus vulgaris, vesiculobullous or erosive lichen planus, Behçet syndrome, recurrent aphthous stomatitis, and primary herpetic gingivostomatitis. Serum sickness–like reaction to cefaclor (or other antibiotics) may also manifest as EM-like lesions; the lesions may develop a dusky to purple color, but in most cases, the eruption of cefaclor-induced serum sickness–like reaction is pruritic, transient, and migratory and is probably urticarial rather than true EM.

Treatment
Treatment of EM is supportive. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory agents do not alter the course of the disease but may provide symptomatic relief. For individuals with severe mucosal disease, opioids can be used to control pain and diligent oral hygiene is essential. No controlled, prospective studies support the use of corticosteroids in the management of EM. Prophylactic oral acyclovir given for 6 mo may be effective in controlling recurrent episodes of HSV-associated EM. On discontinuation of acyclovir, both HSV and EM may recur, although episodes may be less frequent and milder. For recurrent cases not responsive to antiviral therapy, steroid-sparing agents used to decrease frequency of recurrence include azathioprine, mycophenolate mofetil, and dapsone. Appropriate laboratory monitoring is recommended.

Bibliography is available at Expert Consult.

654.2 Stevens-Johnson Syndrome
Joel C. Joyce

ETIOLOGY
Drugs, particularly sulfonamides, nonsteroidal antiinflammatory agents, antibiotics, and anticonvulsants, are the most common precipitants of Stevens-Johnson syndrome and toxic epidermal necrolysis. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; see below) exist along a spectrum: SJS is defined as affected body surface area <10%, SJS–TEN overlap syndrome is affected body surface area between 10% and 30%, and TEN is affected body surface area >30%. TEN is the most-severe disorder in the clinical spectrum of the disease, involving considerable constitutional toxicity and extensive necrolysis of the mucous membranes and >30% of the body surface area. Human leukocyte antigen (HLA)-B*1502 and HLA-B*5801 are implicated in the development of these 2 disorders in Han Chinese patients receiving carbamazepine and in Japanese patients receiving allopurinol, respectively.

Infections, particularly in children, also are associated with SJS, although current thinking defines most cases of classic SJS as secondary to medications. Terms such as “M. pneumoniae-associated mucositis” or “atypical SJS” have caused difficulty with diagnosis and classification. Individuals, typically children or young adults, often with upper respiratory symptoms from M. pneumoniae infection, suffer from variable degrees of mucosal ulceration and erosion (typically mouth but including other mucosae) but lack other cutaneous involvement (unlike traditional SJS-TEN) and are found to have evidence of infection with M. pneumoniae, typically by polymerase chain reaction evaluation. In addition to supportive treatment below, affected individuals benefit from antimicrobial treatment for M. pneumoniae. Morbidity is typically less severe than for SJS-TEN spectrum disease.

Clinical Manifestations
Cutaneous lesions in SJS generally consist initially of erythematous macules that rapidly and variably develop central necrosis to form vesicles, bullae, and areas of denudation on the face, trunk, and extremities. The skin lesions are typically more widespread than in EM and are accompanied by involvement of 2 or more mucosal surfaces, namely the eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa (Fig. 654-3). A burning sensation, edema, and erythema of the lips and buccal mucosa are often the presenting signs, followed by development of bullae, ulceration, and hemorrhagic crusting. Lesions may be preceded by a flu-like upper respiratory illness. Pain from mucosal ulceration is often severe, but skin tenderness is minimal to absent in SJS, in contrast to pain in TEN. Corneal ulceration, anterior uveitis, panophthalmitis, bronchitis, pneumonia, myocarditis, hepatitis, enterocolitis, polyarthritis, hematuria, and acute tubular necrosis leading to renal failure may occur. Disseminated cutaneous bullae and erosions may result in increased insensible fluid loss and a high risk of bacterial superinfection and sepsis. New lesions occur in crops, and complete healing may take 4-6 wk; ocular scarring, visual impairment, and strictures of the
**Bibliography**


esophagus, bronchi, vagina, urethra, or anus may remain. Nonspecific laboratory abnormalities in SJS include leukocytosis, elevated erythrocyte sedimentation rate, and, occasionally, increased liver transaminase levels and decreased serum albumin values.

Pathogenesis
Pathogenesis is related to drug-specific CD8+ cytotoxic T cells, with perforin/granzyme B and granulysin triggering keratinocyte apoptosis. This process is followed by expanded enactment of apoptosis involving the interaction of soluble Fas ligand with Fas receptor. Recently, consideration has been given to the role that macrophages/monocytes play in development of SJS/TEN via tumor necrosis factor-α, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor–inducer of apoptosis weak (TWEAK) signaling pathways. It is likely that many affected individuals have yet unrecognized underlying genetic predispositions.

Differential Diagnosis
The differential diagnosis of SJS includes TEN, urticaria, M. pneumoniae–associated mucositis, DRESS (drug rash [or reaction] with eosinophilia and systemic symptoms) syndrome (see Chapter 645.2) and other drug eruptions and viral exanthems, including Kawasaki disease. SJS has rarely been reported in patients with systemic lupus erythematosus.

Treatment
Management of SJS is supportive and symptomatic. Potentially offending drugs must be discontinued as soon as possible. Ophthalmologic consultation is mandatory because ocular sequelae such as corneal scarring can lead to vision loss. Application of cryopreserved amniotic membrane to the ocular surface during the acute phase of the disease limits the destructive and long-term sequelae. Early topical steroid treatment may also reduce ocular sequelae. Oral lesions should be managed with mouthwashes and glycerin swabs. Vaginal lesions should be observed closely and treated to prevent vaginal stricture or fusion. Topical anesthetics (diphenhydramine, dyclonine, viscous lidocaine) may provide relief from pain, particularly when applied before eating. Denuded skin lesions can be cleansed with saline or Burrow solution compresses. Antibiotic therapy is appropriate for documented secondary bacterial infection. Treatment may require admission to an intensive care unit; IV fluids; nutritional support; sheepskin or air-fluid bedding; daily saline or Burrow solution compresses; paraffin gauze or colloidal gel (Hydrogel) dressing of denuded areas; saline compresses on the eyelids, lips, or nose; analgesics; and urinary catheterization (when needed). A daily examination for infection and ocular lesions, which constitute the major cause of long-term morbidity, is essential. Systemic antibiotics are indicated for documented urinary or cutaneous infections and for suspected bacteremia (Staphylococcus aureus or Pseudomonas aeruginosa) because infection is the leading cause of death. Prophylactic systemic antibiotics are not necessary. Although corticosteroids are sometimes advocated in early, severe cases of SJS, no prospective double-blind studies evaluating their efficacy have been reported. Most authorities discourage their use because of reports of increased morbidity and mortality (sepsis) with their administration, although definitive trials in children are lacking. IV immunoglobulin (IVIG; 1.5-2.0 g/kg/day × 3 days) should be considered in early disease. Total dose greater than 2 g/kg has shown improved but not statistically significant outcomes in children compared to adults. Other immunosuppressive treatment regimens have not demonstrated clear benefit or repeated success in multiple controlled studies.

Bibliography is available at Expert Consult.

Figure 654-3 Bullae are present on the conjunctivae (A) and in the mouth (B) with Stevens-Johnson syndrome. C, Sloughing, ulceration, and necrosis in the oral cavity interfere with eating. Genital lesions cause dysuria and interfere with voiding. (From Habif TP, editor: Clinical dermatology, ed 4, Philadelphia, 2004, Mosby, p. 631.)

654.3 Toxic Epidermal Necrolysis
Joel C. Joyce

Epidemiology and Etiology
The pathogenesis of TEN is not proved but may involve a hypersensitivity phenomenon that results in damage primarily to the basal cell layer of the epidermis. Epidermal damage appears to result from keratinocyte apoptosis (see Chapter 654.2). This condition is triggered by many of the same factors that are thought to be responsible for SJS, principally drugs such as the sulfonamides, amoxicillin, phenobarbital, hydantoin, and allopurinol. TEN is defined by (1) widespread blisters formation and morbilliform or confluent erythema, associated with skin tenderness; (2) absence of target lesions; (3) sudden onset and generalization within 24-48 hr; (4) histologic findings of full-thickness epidermal necrosis and a minimal-to-absent dermal infiltrate. These criteria categorize TEN as a separate entity from EM.

Clinical Manifestations
The prodrome consists of fever, malaise, localized skin tenderness, and diffuse erythema. Inflammation of the eyelids, conjunctivae, mouth, and genitals may precede skin lesions. Flaccid bullae may develop,
Bibliography


Narcotics are often required for pain relief. Mouth and eye care, as for EM major and SJS, may be necessary. Because of an immune mechanism, systemic glucocorticosteroids and IVIG have been used with apparent success. Nonetheless, this treatment remains controversial although trends toward decreased morbidity and mortality in children receiving high-dose IVIG have been demonstrated (see Chapter 654.2).

Bibliography is available at Expert Consult.

654.4 Mechanobullous Disorders
Joel C. Joyce

EPIDERMOLYSIS BULLOSA

Diseases categorized under the general term epidermolysis bullosa (EB) are a heterogeneous group of congenital, genetic blistering disorders. They differ in severity and prognosis, clinical and histologic features, and inheritance patterns but are all characterized by induction of blisters by trauma and exacerbation of blistering in warm weather. The disorders can be categorized under 3 major headings with multiple subgroupings: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB) (Table 654-2).

Kindler syndrome, which includes poikiloderma and photosensitivity as well as easy blistering, is also considered a separate form of EB. Epidermolysis bullosa acquisita is an autoimmune disorder producing antibodies to the α chain of type VII collagen. Affected mothers may pass the autoantibody to the fetus resulting in similar but transient lesions in the newborn.

EPIDERMOLYSIS BULLOSA SIMPLEX

EBS is a nonscarring, autosomal dominant disorder. The defect in most common types of EBS is in keratin 5 or 14, which makes up intermediate filaments of the basal keratinocytes. The intraepidermal bullae result from cytolysis of the basal cells. There are multiple other rare variants with defects that also result in intraepidermal blistering.

In EBS—generalized other (formerly Koebner), bullae are usually present at birth or during the neonatal period. Sites of predilection are the hands, feet, elbows, knees, legs, and scalp. Intraoral lesions may be covered with a semipermeable dressing.

Anticonvulsant hypersensitivity syndrome (DRESS syndrome; see Chapter 645.2) is a multisystem reaction that appears approximately 3 wk to 3 mo after the start of therapy with the offending agent. The skin eruption is red-pink morbilliform eruption often associated with facial swelling, lymphadenopathy, fever, hepatic, renal, and pulmonary disease, eosinophilia, atypical lymphocytosis, and leukocytosis.

TREATMENT

Appreciation of the specific etiologic factor is crucial. As most cases are drug-induced, cessation of the offending agent is critical as soon as possible. Management is similar to that for severe burns and may be best accomplished in a burn unit (see Chapter 75). It may include strict reverse isolation, meticulous fluid and electrolyte therapy, use of an air-fluid bed, and daily cultures. Systemic antibiotic therapy is indicated when secondary infection is evident or suspected. Skin care consists of cleansing with isotonic saline or Burrow solution. Biologic or colloid gel (Hydrogel) dressings alleviate pain and reduce fluid loss.
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AD, autosomal dominant; AR, autosomal recessive; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; EM, electron microscopy; GI, gastrointestinal; IF, immunohistochemical and immunofluorescence antigen mapping findings.

Part XXXI ◆ The Skin

Mucous membrane involvement may be severe, and ulceration of the respiratory, gastrointestinal, and genitourinary epithelium has been documented in many affected children, although less frequently than in severe recessive dystrophic epidermolysis bullosa. Healing is delayed, and vegetating granulomas may persist for a long time. Large, moist, erosive plaques (Fig. 654-7) may provide a portal of entry for bacteria, and septicemia is a frequent cause of death. Mild atrophy may be seen in areas of recurrent blistering. Defective dentition with early loss of teeth as a result of rampant caries is characteristic. Growth retardation and calcificranic anemia are almost invariable. In addition to infection, cachexia and circulatory failure are common causes of death. Most patients die within the 1st 3 yr of life.

**JEB–non-Herlitz** is a heterogeneous group of disorders. Blistering may be severe in the neonatal period, making differentiation from the Herlitz type difficult. All conditions associated with the Herlitz type may be seen but are usually milder. **JEB–non-Herlitz generalized** (formerly generalized atrophic benign EB) is included as a variant of non-Herlitz JEB. Another variant of non-Herlitz JEB is associated with **pyloric atresia**.

In all types of JEB, a subepidermal blister is found on light microscopic examination, and electron microscopy demonstrates a cleavage plane in the lamina lucida, between the plasma membranes of the basal cells and the basal lamina. Absence or a great reduction of hemidesmosomes is seen on electron micrographs in **JEB–Herlitz** and some cases of **JEB–non-Herlitz**. The defect is in laminin 332 (formerly laminin 5 or epiligrin), a glycoprotein associated with anchoring filaments beneath the hemidesmosomes. In **JEB–non-Herlitz**, defects have also been described in other hemidesmosomal components, such as type XVII collagen (BP180). In **JEB–pyloric atresia**, the defect is in the αβ integrin.

**Treatment** for JEB is supportive. The diet should provide adequate calories and supplemental iron. Infections should be treated promptly. Transfusions of packed red blood cells may be required if the patient shows no response to iron and erythropoietin therapy. Strict adherence to wound care regimens is essential. Tissue-engineered skin grafts (artificial skin derived from human keratinocytes and fibroblasts) may be beneficial.

**DYSTROPHIC EPIDERMOLYSIS BULLOSA**

All forms of DEB result from mutations in collagen VII, a major component of anchoring fibrils that tether the basement membrane and overlying epidermis to its dermal foundation. The blister is subepidermal in all types of DEB. The type and location of the mutation dictate the severity of the phenotype.

**Dominant DEB** is the most common type of DEB. The spectrum of dominant DEB is varied. Blisters may be manifest at birth and are often limited and characteristically form over acral bony prominences. The lesions heal promptly, with the formation of soft, wrinkled scars, milia, and alterations in pigmentation (Fig. 654-8). Abnormal nails and nail loss are common. In many cases, the blistering process is mild, causing little restriction of activity and not impairing growth and development. Mucous membrane involvement tends to be minimal.
Although the skin becomes less sensitive to trauma with aging in patients with recessive DEB, the progressive and permanent deformities complicate management, and the overall prognosis is poor. Foods that traumatize the buccal or esophageal mucosa should be avoided. If esophageal scarring develops, a semiliquid diet and esophageal dilations may be required. Stricture excision or colonic interposition may be needed to relieve esophageal obstruction. In infants, severe oropharyngeal involvement may necessitate the use of special feeding devices such as a gastrostomy tube. Iron therapy for anemia, intermittent antibiotic therapy for secondary infections, and periodic surgery for release of digits may reduce morbidity. Newer generation wound care dressings, including non-stick dressings made from silicone, are a mainstay of treatment and the daily maintenance of the skin barrier to reduce new skin trauma and promote healing. Tissue-engineered skin grafts containing keratinocytes and fibroblasts are of some benefit. Transdermal gene therapy with allogeneic fibroblasts and the delivery of functional collagens is being pursued. Allogeneic bone marrow transplantation may also be beneficial as may the induction of pluripotent stem cells.

KINDLER SYNDROME

Kindler syndrome, often considered a distant subtype of EB, contains features of both EB such as congenital blistering, and features of the congenital poikiloderma, such as Rothmund-Thomson syndrome and Bloom syndrome (see Chapter 656), which include photosensitivity, congenital poikiloderma, and progressive cutaneous atrophy. Blisters tend to appear on acral sites in infancy or early childhood and are provoked by trauma. Photosensitivity can appear as increased susceptibility to sunburn. Both blistering and photosensitivity can improve greatly with advancing age, but poikilodermatous changes can be progressive. Sclerodermoid-like changes and nail abnormalities of the hands and feet as well as dental abnormalities have been reported.

Kindler syndrome is an autosomal recessive disorder caused by mutations in \textit{KIND1} (also known as \textit{FERMT1}), which encodes kindlin-1, a protein thought to regulate interactions between the extracellular matrix and actin filaments. Blister formation has been shown to occur within the epidermis, within the basement membrane zone, and below the basement membrane. As Kindler syndrome is often confused with EB, at least initially, it can be confirmed by electron microscopy, immunostaining for anti-kindlin-1 antibodies within the skin, or by mutation analysis of the \textit{KIND1} gene.

Treatment is similar to that for EB above, with efforts to reduce trauma to the skin, meticulous wound care, and treatment of skin infections. In addition, sun avoidance measures are beneficial as they can slow the rate of the development of poikiloderma.

Bibliography is available at Expert Consult.

654.5 Pemphigus

Joel C. Joyce

PEMPBHIGUS VULGARIS

Etiology/Pathogenesis

Pemphigus vulgaris (PV) is a rare autoimmune blistering disorder caused by circulating antibodies to desmoglein III that result in suprabasal cleaving with consequent blister formation. Desmoglein III is a 30-kDa glycoprotein that is complexed with plakoglobin, a plaque protein of desmosomes. The desmogleins are a subfamily of the cadherin family of cell adhesion molecules.

Clinical Manifestations

PV usually first appears as painful oral ulcers, which may be the only evidence of the disease for weeks or months. Subsequently, large, flaccid bullae emerge on nonerythematous skin, most commonly on the face, trunk, pressure points, groin, and axillae. The Nikolsky sign
Bibliography


is present. The lesions rupture and enlarge peripherally, producing painful, raw, denuded areas that have little tendency to heal. When healing occurs, it is without scarring, but hyperpigmentation is common. Malodorous, verrucous, and granulomatous lesions may develop at sites of ruptured bullae, particularly in the skinfolds; as this pattern becomes more pronounced, the condition may be more properly referred to as pemphigus vegetans. Because the course may rapidly lead to debility, malnutrition, and death, prompt diagnosis is essential. Neonatal PV develops in utero as a result of placental transfer of maternal antidesmoglein antibodies from women who have active PV, although it may occur when the mother is in remission. High antepartum maternal titers of PV antibodies and increased maternal disease activity correlate with a poor fetal outcome, including demise.

Pathology
Biopsy of a fresh small blister reveals a suprabasal (intraepidermal) blister containing loose, acantholytic epidermal cells that have lost their intercellular bridges and thus their contact with one another. Immunofluorescence staining with an IgG antibody produces a characteristic pattern (“chicken wire”) on direct immunofluorescence preparations of both involved and uninvolved skin of essentially all patients. Serum IgG antibody titers to desmoglein correlate with the clinical course in many patients; thus, serial determinations may have predictive value.

Differential Diagnosis
PV must be differentiated from EM, bullous pemphigoid, SJS, and TEN.

Treatment
The disease is best treated initially with systemic methylprednisolone 1-2 mg/kg/day. Azathioprine, cyclophosphamide, and methotrexate therapy all have been useful in maintenance regimens. IVIG given in cycles may be beneficial to patients whose disease does not respond to steroids. Rituximab with IVIG replacement has been effective in the management of severe pemphigus. Excellent control of the disease may be obtained, but relapse is common. It has been successfully used in children.

Pemphigus foliaceus

Etiology/Pathogenesis
Pemphigus foliaceus is caused by circulating antibodies to a 50-kDa portion of the 160-kDa desmosomal glycoprotein desmoglein I, which result in subcorneal cleavage leading to superficial erosions. This extremely rare disorder is characterized by subcorneal blistering; the site of cleavage is high in the epidermis rather than suprabasal as in PV.

Clinical Manifestations
The superficial blisters rupture quickly, leaving erosions surrounded by erythema that heal with crusting and scaling (Fig. 654-11). The Nikolsky sign is present. Focal lesions are usually localized to the scalp, face, neck, and upper trunk. Mucous membrane lesions are minimal or absent. Pruritus, pain, and a burning sensation are frequent complaints. The clinical course varies but is generally more benign than that of PV. Fogo selvagem (endemic pemphigus foliaceus), which is endemic in certain areas of Brazil, is identical clinically, histopathologically, and immunologically to pemphigus foliaceus. Recently, it was shown that anti-desmoglein-1 antibodies in individuals with fogo selvagem crossreact with sand fly (Lutzomyia sp.) salivary proteins, suggesting an environmental trigger for this autoimmune disease.

Pathology
An intraepidermal acantholytic bulla high in the epidermis is diagnostic. It is imperative to select an early lesion for biopsy. Immunofluorescent staining with an IgG antibody reveals a characteristic intercellular staining pattern similar to that of PV but higher in the epidermis.
and bullous impetigo, which can be differentiated by histologic examination, immunofluorescence studies, and cultures. The large, tense bullae of BP can generally be distinguished from the smaller, flaccid bullae of PV.

**Treatment**
Localized bullous pemphigoid can be successfully suppressed with superpotent topical corticosteroids twice a day. Generalized disease usually requires systemic methylprednisolone (1 mg/kg/day) therapy. Rarely are other immunosuppressive treatments necessary, such as azathioprine or mycophenolate mofetil. Refractory cases have been treated with rituximab, but the condition usually remits within a year in most children.

*Bibliography is available at Expert Consult.*

**654.6 Dermatitis Herpetiformis**

Joel C. Joyce

**ETIOLOGY/PATHOGENESIS**
In dermatitis herpetiformis (DH), IgA antibodies are directed at epidermal transglutaminase (transglutaminase 3). **Gluten-sensitive enteropathy** (celiac disease) is found in all patients with DH, although the majority are asymptomatic or have minimal gastrointestinal symptoms (see Chapter 338.2). The severity of the skin disease and the responsiveness to gluten restriction do not correlate with the severity of the intestinal inflammation. An antibody to smooth muscle endomysium is found in 70-90% of patients with DH. Ninety percent of patients with the disease express HLA-DQ2. HLA-DQ2-negative patients with DH usually express HLA-DQ8.

**CLINICAL MANIFESTATIONS**
DH is characterized by symmetric, grouped, small, tense, erythematous, stinging, intensely pruritic papules and vesicles. The eruption is pleomorphic, including erythematous, urticarial, papular, vesicular, and bullous lesions. Sites of predilection are the knees, elbows, shoulders, buttocks, forehead, and scalp; mucous membranes are usually spared. Hemorrhagic lesions may develop on the palms and soles. When pruritus is severe, excoriations may be the only visible sign (Fig. 654-12).

**PATHOLOGY**
Subepidermal blisters composed predominantly of neutrophils are found in dermal papillae. The presence of granular IgA on direct immunofluorescence in the dermal papillary tips is diagnostic.

**DIFFERENTIAL DIAGNOSIS**
DH may mimic other chronic blistering diseases and may also resemble scabies, papular urticaria, insect bites, contact dermatitis, and papular eczema.

**TREATMENT**
Patients with DH show response within weeks to months to a gluten-free diet. Oral administration of dapsone (0.5-2.0 mg/kg/day divided qd or bid) provides immediate relief from the intense pruritus but must be used with caution because of possible serious side effects (methemoglobinemia, hemolysis, and hypersensitivity syndrome [sulfone syndrome]). Dapsone alone may not relieve the intestinal inflammation of celiac disease. Local antipruritic measures may also be useful. Jejunal biopsy is indicated to diagnose gluten-sensitive enteropathy, because cutaneous manifestations may precede malabsorption. The disease is chronic and either a gluten-free diet or dapsone must be continued indefinitely to prevent relapse.

*Bibliography is available at Expert Consult.*

**654.7 Linear Immunoglobulin A Dermatosis (Chronic Bullous Dermatosis of Childhood)**

Joel C. Joyce

**ETIOLOGY/PATHOGENESIS**
Linear IgA dermatosis is a heterogeneous autoimmune disorder with antibodies targeting multiple antigens. It is caused by circulating IgA antibodies, most commonly to LABD97 and LAD-1, which are degradation proteins of BP180 (type XVII collagen). Linear IgA dermatosis may also be seen as a drug eruption. Most cases of drug-induced linear IgA dermatosis are related to vancomycin, although anticonvulsants, ampicillin, cyclosporine, and captopril are implicated.

**CLINICAL MANIFESTATIONS**
This rare dermatosis is most common in the 1st decade of life, with a peak incidence during the preschool years. The eruption consists of many large symmetrically located, tense bullae filled with clear or hemorrhagic fluid. The bullae are often clustered together and develop on a normal or erythematous, urticarial base. Areas of predilection are the genitals and buttocks (Fig. 654-13), the perioral region, and the scalp. Sausage-shaped bullae may be arranged in an annular or rosette-like fashion around a central crust (Fig. 654-14). Erythematous plaques with gyrate margins bordered by intact bullae may develop over larger areas. Pruritus may be absent or very intense, and systemic signs or symptoms are absent.

**PATHOLOGY**
The subepidermal bullae are infiltrated with a mixture of inflammatory cells. Neutrophilic abscesses may be noted in the dermal papillary tips, indistinguishable from those of DH. The infiltrate may also be largely eosinophilic, resembling that in BP. Therefore, direct immunofluorescence studies are required for a definitive diagnosis of linear IgA dermatosis; perilesional skin demonstrates linear deposition of IgA and sometimes IgG and C3 at the dermal–epidermal junction. Immunoelectron microscopy has localized the immunoreactants to the sublamina densa, although a combined sublamina densa and lamina lucida pattern has also been seen.

**DIFFERENTIAL DIAGNOSIS**
The eruption can be distinguished by histopathologic and immunofluorescence studies from pemphigus, BP, DH, and EM. Gram stain and culture preclude the diagnosis of bullous impetigo.
Bibliography
Bibliography

TREATMENT
Many cases of linear IgA dermatosis respond favorably to oral dapsone (see treatment of DH) or sulfapyridine. Other antibiotics, including erythromycin and dicloxacillin have been used, but the response is often transient. Children who show no response to dapsone may benefit from oral therapy with methylprednisolone (1 mg/kg/day) or a combination of these drugs. The usual course is 2-4 yr, although some children have persistent or recurrent disease; there are typically no long-term sequelae. IgA nephropathy is a rare complication.

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


Eczematous skin disorders are a broad group of cutaneous eruptions characterized by erythema, edema, and pruritus. Acute eczematous lesions demonstrate erythema, weeping, oozing, and the formation of microvesicles within the epidermis. Chronic lesions are generally thickened, dry, and scaly, with coarse skin markings (lichenification) and altered pigmentation. Many types of eczema occur in children; the most common is atopic dermatitis (see Chapter 145), although seborrheic dermatitis, allergic and irritant contact dermatitis, nummular eczema, and acute palmoplantar eczema (dyshidrosis) are also relatively common in childhood.

Once the diagnosis of eczema has been established, it is important to classify the eruption more specifically for proper management. Pertinent historical data often provide the clue. In some instances, the subsequent course and character of the eruption permit classification. Histologic changes are relatively nonspecific, but all types of eczematous dermatitis are characterized by intraepidermal edema known as spongiosis.

655.1 Contact Dermatitis

The form of eczema known as contact dermatitis can be subdivided into irritant dermatitis, in which nonspecific injury to the skin causes immediate inflammation, and allergic contact dermatitis, resulting from a delayed hypersensitivity reaction. Irritant dermatitis is more frequent in children, particularly during the early years of life. Allergic reactions increase in frequency upon maturation of the immune system.

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis can result from prolonged or repetitive contact with physical, chemical, or mechanical irritants, including saliva, urine, feces, fragrance, detergents, dyes, henna, plants, caterpillars, abrasive materials, and chafing.

Irritant contact dermatitis may be difficult to distinguish from atopic dermatitis or allergic contact dermatitis. A detailed history and consideration of the sites of involvement, the age of the child, and contactants usually provide clues to the etiologic agent. The propensity for development of irritant dermatitis varies considerably among children; some may respond to minimal injury, making it difficult to identify the offending agent through history. Children with atopic dermatitis are more prone to irritant contact dermatitis as an exacerbating factor. Irritant contact dermatitis usually clears after removal of the stimulus and temporary treatment with a topical corticosteroid preparation (see Chapter 646). Education of patients and parents about the causes of contact dermatitis is crucial to successful therapy.

Dry skin dermatitis results from repetitive wet-to-dry behaviors such as lip-licking (Fig. 655-1), thumb-sucking, frequent hand washing, or excessive sweating. Involved skin is erythematous and fissured, localized to the area of exposure. Treatment of dry skin dermatitis begins with eliminating the offending wet-to-dry behavior. Moisturizer cream applied twice daily decreases transepidermal water loss and replenishes skin lipids to improve hydration. A topical steroid is usually necessary to treat the inflammation.

Juvenile plantar dermatosis occurs mainly in prepubertal children with hyperhidrosis who wear occlusive synthetic footwear. Weight-bearing surfaces of the foot may be pruritic or painful and
Diaper dermatitis often responds to simple measures; some infants are predisposed to diaper dermatitis, and management may be difficult. The damaging effects of overhydration of the skin and prolonged contact with feces and urine can be obviated by frequent changing of the diapers and periods of “rest” free of diaper use. Cleansing of affected skin is best accomplished with a soft cloth and lukewarm water, patted dry. Overwashing should be avoided because it leads to chapping and a worsening of the dermatitis. Disposable diapers containing a superabsorbent material may help maintain a relatively dry environment. First-line therapy for diaper dermatitis is application of a protective barrier agent (ointment or paste) containing petroleum or zinc oxide at every diaper change. Topical sulfacetamide is an effective barrier with some antibacterial activity, useful for recalcitrant cases. Low-potency nonhalogenated topical corticosteroids, such as 2.5% hydrocortisone, may be used for short time periods (1-2 wk). Treatment with a topical anticandidal agent is indicated for secondary candidal infection. Topical preparations containing triamcinolone-nystatin and betamethasone dipropionate-clotrimazole are generally inappropriate for diaper dermatitis in infants because of the higher potency of the corticosteroid component. If using multiple topical agents, the protective barrier should be applied last. When diaper dermatitis does not respond to typical prevention and treatment strategies, non–diaper-associated causes must be considered.

**ALLERGIC CONTACT DERMATITIS**

Allergic contact dermatitis is common in childhood and should be considered in any child with recalcitrant eczema. This is a T-cell–mediated hypersensitivity reaction that is provoked by application of an antigen to the skin surface. The antigen penetrates the skin, where it is conjugated with a cutaneous protein, and the hapten–protein complex is transported to the regional lymph nodes by antigen-presenting Langerhans cells. A primary immunologic response occurs locally in the nodes and becomes generalized, presumably because of dissemination of sensitized T cells. Sensitization requires several days and, when followed by a fresh antigenic challenge, manifests as allergic contact dermatitis. Generalized distribution may also occur if enough antigen finds its way into the circulation, such as by consumption. Once sensitization has occurred, each new antigenic challenge may provoke an inflammatory reaction within 8-12 hr; sensitization to a particular antigen usually persists for many years.
Acute allergic contact dermatitis is an erythematous, intensely pruritic, eczematous dermatitis. Acute cases may be edematous and vesiculobullous. The chronic condition has the features of long-standing eczema: lichenification, scaling, fissuring, and pigmentary change. The distribution of the eruption often provides a clue to the diagnosis. Airborne sensitizers usually affect exposed areas, such as the face and arms. Jewelry, topical agents, shoes, clothing, henna tattoo dyes, plants, and even toilet seats cause dermatitis at points of contact.

*Rhus dermatitis* (poison ivy, poison sumac, poison oak), a response to the plant allergen urushiol, is the most common allergic contact dermatitis. It is often vesiculobullous and may be distinguished by linear streaks of vesicles where the plant leaves have brushed against the skin (Fig. 655-4). Fluid from ruptured cutaneous vesicles does not spread the eruption; antigen retained on skin, clothing, or under fingernails initiates new plaques of dermatitis if not removed by washing with soap and water. Antigen may also be carried by animals on their fur. "Black spot" poison ivy dermatitis is a rare variant that results from oxidation of concentrated urushiol left on the skin and manifests as small discrete black lacquer–like glossy papules with surrounding erythema and edema. Sensitization to 1 plant produces crossreactions with the others. Spontaneous resolution occurs in 1-3 wk, with the most common complication being secondary bacterial infection with normal skin flora. Exposure avoidance and thorough washing after exposure are the mainstays for prevention. Barrier creams or organo-clay compounds such as bentoquatam may be effective if applied prior to expected exposure.

*Nickel dermatitis* develops from contact with jewelry, metal closures on clothing, or even cell phones. Metal closures on pants frequently cause periumbilical dermatitis (Fig. 655-5). Some children are exquisitely sensitive to nickel, with even the trace amounts found in gold jewelry provoking eruptions. The most frequently involved sites from jewelry are the earlobes from nickel-containing earrings. Early ear piercing increases risk of sensitization, and it is recommended to delay piercing until after 10 yr of age. Patch testing for nickel sensitivity is unreliable in infants and toddlers and should only be performed if there is high clinical suspicion.

*Shoe dermatitis* typically affects the dorsum or soles of the feet and toes, sparing the interdigital spaces; it is usually symmetric. Other forms of allergic contact dermatitis, in contrast to irritant dermatitis, rarely involve the palms and soles. Common allergens are the antioxidants and accelerators in shoe rubber, adhesives, and the chromium salts in tanned leather or shoe dyes. Excessive sweating often leaches these substances from their source.

Apparel contains a number of sensitizers, including dyes, dye fixative, fabric finishes, fibers, resins, and cleaning solutions. Dye may be poorly fixed to clothing and so may be leached out with sweating, as can partially cured formaldehyde resins. The elastic in garments is a frequent cause of clothing dermatitis, and contact allergy to the ink "tag" of tagless baby clothing has been reported. Exposure to other items with fabric, such as infant car seats, may induce reactions similar to clothing.

Topical medications and cosmetics may be unsuspected as allergens, particularly if a medication is being used for a preexisting dermatitis. The most common offenders are neomycin, topical antihistamines, topical anesthetics, fragrances, topical corticosteroids, oxybenzone and octocrylene in chemical sunscreens, preservatives, dye in temporary tattoos, and ethylenediamine, a stabilizer present in many medications. All types of cosmetics can cause facial dermatitis; involvement of the eyelids is characteristic for nail polish sensitivity.

Neomycin sulfate is present in many nonprescription topical antibiotic preparations, and thus children are frequently exposed at an early age. It is one of the most common causes of allergic contact dermatitis, and use of combination products of neomycin with other antibiotics, antifungals, or corticosteroids may induce co-reactivity with these chemically-unrelated substances.

Diagnosis of allergic contact dermatitis is usually based on history; however, patch testing may be helpful, especially in older children. Identification and avoidance of the offending agent is the mainstay of
managing allergic contact dermatitis. First-line treatment for acute eruption is with midpotency topical corticosteroid ointment for 2-3 wk, as well as symptom management with wet dressings and sedating antihistamines to allow for sleep. Systemic corticosteroids are used when >10% of skin is involved (0.5-1.0 mg/kg prednisone for 7-10 days, followed by a 7-10 day taper). More chronic allergic contact dermatitis is treated with low- to midpotency topical corticosteroids. Desensitization therapy is rarely indicated. Differential diagnosis of allergic contact dermatitis includes herpes simplex virus, impetigo, cellulitis, atopic dermatitis, irritant contact dermatitis, and dermatophytoses.

Bibliography is available at Expert Consult.

655.2 Nummular Eczema
Brianne Z. Dickey and Yvonne E. Chiu

Nummular eczema is characterized by coin-shaped, severely pruritic, eczematous plaques, commonly involving the extensor surfaces of the extremities (Fig. 655-6), buttocks, and shoulders with facial sparing. The plaques are relatively discrete, boggy, vesicular, slightly scaly, and exudative; when chronic, they often become thickened and lichenified, and may develop central clearing. The etiology remains unclear, although nummular eczema possibly represents an atypical morphology of atopic dermatitis. Flares are generally sporadic but may be precipitated by xerosis, irritants, allergens, or occult staphylococcal infection. Most frequently, these lesions are mistaken for tinea corporis, but plaques of nummular eczema are distinguished by the lack of a raised, sharply circumscribed border, the lack of fungal organisms on a potassium hydroxide (KOH) preparation, and frequent weeping or bleeding when scraped. First-line treatment is with emollients, wet dressings, and potent topical corticosteroids. Steroid-impregnated tapes may simultaneously treat and provide barrier protection to these circumscribed eczematous plaques. An oral antihistamine may be helpful, particularly a sedating antihistamine at night. Antibiotics are indicated for secondary infection.

Bibliography is available at Expert Consult.

655.3 Pityriasis Alba
Brianne Z. Dickey and Yvonne E. Chiu

Pityriasis alba occurs mainly in children and causes lesions that are hypopigmented, ill-defined, round or oval patches (Fig. 655-7). They may be mildly erythematous and finely scaly. Lesions occur on the face, neck, upper trunk, and proximal portions of the arms, and are most pronounced on darker skin tones or after tanning of surrounding skin. Itching is minimal or absent. The cause is unknown, but the eruption appears to be exacerbated by dryness and is often regarded as a mild form of eczema. Pityriasis alba is frequently misdiagnosed as vitiligo, tinea versicolor, or tinea corporis. The lesions wax and wane but eventually disappear, and normal pigmentation often takes months to return. Application of a lubricant or emollient may ameliorate the condition. If pruritus is troublesome, a low-potency topical steroid or calcineurin inhibitor may be used.

Bibliography is available at Expert Consult.

655.4 Lichen Simplex Chronicus
Brianne Z. Dickey and Yvonne E. Chiu

Lichen simplex chronicus is a secondary skin disorder resulting from excessive scratching. It is characterized by a chronic pruritic, eczematous, circumscribed plaque that is usually lichenified and hyperpigmented (Fig. 655-8). All affected areas must be accessible to scratching, with the most common sites being the posterior neck, genitalia, wrists, ankles, and dorsal feet. Although the initiating event may be a transient lesion such as an insect bite, trauma from rubbing and scratching accounts for persistence of the plaque. Pruritus must be controlled to
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Bibliography
permit healing, thus a covering to prevent scratching may be necessary. A high potency topical corticosteroid under occlusion is often helpful. Second-line therapy includes adding 6% salicylic acid gel to the topical corticosteroid preparation.

### 655.5 Acute Palmoplantar Eczema
(Dyshidrotic Eczema, Dyshidrosis, Pompholyx)

Brianne Z. Dickey and Yvonne E. Chiu

A recurrent, sometimes seasonal, blistering disorder of the hands and feet, acute palmoplantar eczema occurs in all age groups but is uncommon in infancy. The pathogenesis is unknown, although possible predisposing factors include a history of atopy, exposure to contact allergens or irritants, or IV immunoglobulin therapy. The disease is characterized by recurrent crops of small, deep-seated "tapioca-like" vesicles, which are intensely pruritic and may coalesce into tense bullae (Fig. 655-9). Sites of predilection are the palms, soles, and lateral aspects of the fingers and toes. Primary lesions are noninflammatory and are filled with clear fluid, which, unlike sweat, has a physiologic pH and contains protein. Maceration and secondary infection are frequent because of scratching. The chronic phase is characterized by thickened, fissured plaques that may cause considerable discomfort, as well as dystrophic nails. Hyperhidrosis is common in many patients, but the association may be fortuitous. The diagnosis is made clinically. The disorder may be confused with allergic contact dermatitis, which usually affects the dorsal rather than the volar surfaces, and with dermatophytosis, which can be distinguished by a KOH preparation of the roof of a vesicle and by appropriate cultures.

Acute palmoplantar eczema responds to wet dressings, liberal emollient use, and potent topical corticosteroid ointment applied twice daily for 2-4 wk. Weeping skin benefits from twice daily soaking in an astringent solution, such as aluminum subacetate. Second-line treatment is topical tacrolimus 0.1% ointment. Severe disease may require oral corticosteroids with 2 wk taper, or even psoralen UVA therapy. Control of the chronic stage is difficult; lubricants containing mild keratolytic agents in conjunction with a potent topical fluorinated corticosteroid preparation may be indicated. Secondary bacterial infection should be treated systemically with an appropriate antibiotic. Patients should be told to expect recurrence and should protect their hands and feet from the damaging effects of excessive sweating, chemicals, harsh soaps, and adverse weather. Unfortunately, it is impossible to prevent recurrence or to predict its frequency.

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### 655.6 Seborrheic Dermatitis

Brianne Z. Dickey and Yvonne E. Chiu

**ETIOLOGY**

Seborrheic dermatitis is a chronic inflammatory disease most common in infancy and adolescence that parallels the distribution, size, and activity of the sebaceous glands. The cause is unknown, as is the role of the sebaceous glands in the disease. *Malassezia furfur* is implicated as a causative agent, although it remains unclear whether dermatis results from the action of the fungus, its byproducts, or an exaggerated response of the host. In adolescence, seborrheic dermatitis typically occurs after puberty, indicating a possible role for sex hormones.

It is also unknown whether infantile seborrheic dermatitis and adolescent seborrheic dermatitis are the same or different entities. There is no evidence that children with infantile seborrheic dermatitis will experience seborrheic dermatitis as adolescents.

**CLINICAL MANIFESTATIONS**

The disorder may begin in the 1st mo of life and typically self-resolves by 1 yr. Diffuse or focal scaling and crusting of the scalp, sometimes called cradle cap (Fig. 655-10), may be the initial and at times the only manifestation. A greasy, scaly, erythematous papular dermatitis, which is usually nonpruritic in infants, may involve the face, neck, retroauricular areas, axillae, umbilicus, and diaper area. The dermatitis may be patchy and focal or may spread to involve almost the entire body (Fig. 655-11). Postinflammatory pigmented changes are common, particularly in black infants. When the scaling becomes pronounced, the condition may resemble psoriasis and, at times, can be distinguished only with difficulty. The possibility of coexistent atopic dermatitis must be considered when there is an acute weeping dermatitis with pruritus, and the two are often clinically inseparable at an early age. An intractable seborrhea-like dermatitis with chronic diarrhea and failure to thrive may reflect systemic dysfunction of the immune system. A chronic seborrhea-like pattern, which responds poorly to treatment, may also result from cutaneous histiocytic infiltrates in infants with Langerhans cell histiocytosis. Seborrheic dermatitis is a common cutaneous manifestation of AIDS in young adults and is characterized by thick, greasy scales on the scalp and large hyperkeratotic erythematous plaques on the face, chest, and genitals.

During adolescence, seborrheic dermatitis is more localized and may be confined to the scalp and intertriginous areas. Also noted may be marginal blepharitis and involvement of the external auditory canal. Scalp changes vary from diffuse, brawny scaling to focal areas of...
thick, oily, yellow crusts with underlying erythema. Loss of hair is common, and pruritus may be absent to marked. When the dermatitis is severe, erythema and scaling occur at the frontal hairline, the medial aspects of the eyebrows, and in the nasolabial and retroauricular folds. Red, scaly plaques may appear in the axillae, inguinal region, gluteal cleft, and umbilicus. On the extremities, seborrheic plaques may be more eczematous and less erythematous and demarcated. Unlike infantile seborrheic dermatitis, adolescent seborrheic dermatitis generally does not self-resolve and has a chronic relapsing course.

Differential Diagnosis

The differential diagnosis of seborrheic dermatitis includes psoriasis, atopic dermatitis, dermatophytosis, histiocytic disorders, and candidiasis. Secondary bacterial infections and superimposed candidiasis are common.

Treatment

Initial management for infantile seborrheic dermatitis is generally conservative given the self-limited nature of this condition. Emollients, baby oil, gentle shampooing with nonmedicated baby shampoo, and gentle use of a soft brush to remove scales are usually effective measures. Persistent lesions may be treated with low-potency topical corticosteroids if inflamed (applied once daily for 1 wk) and a topical antifungal (e.g., ketoconazole 2% cream twice daily). Antifungal shampoos such as ketoconazole 2% shampoo should be used cautiously as they are not tear-free.

First-line therapy for children and adolescents with scalp seborrheic dermatitis is antifungal shampoo used several times weekly to daily (selenium sulfide, ketoconazole, ciclopirox, zinc pyrithione, salicylic acid, or tar). Midpotency topical corticosteroids such as fluocinolone 0.01% shampoo may also be used for inflamed lesions, applied once daily for 2-4 wk. Nonscalp lesions are treated with topical corticosteroid cream (low-potency for facial lesions, midpotency elsewhere), as well as topical antifungals such as ketoconazole 2% cream or ketoconazole 2% shampoo used as a body wash. Second-line therapy for seborrheic dermatitis includes topical calcineurin inhibitors and keratolytic agents such as urea. Severe adult cases improve with oral antifungal agents; however, pediatric studies are lacking. Once acute disease is controlled, antifungal shampoo used on a weekly basis is effective maintenance to reduce risk of relapse.

Bibliography is available at Expert Consult.
Bibliography
Chapter 656  Photosensitivity
Brianne Z. Dickey and Yvonne E. Chiu

Photosensitivity denotes a qualitatively or quantitatively abnormal cutaneous reaction to sunlight or artificial light because of UV radiation. The UV light spectrum contains UVA (320-400 nm wavelength), UVB (290-320 nm wavelength), and UVC (100-290 nm wavelength) subtypes. Transmitted radiation <300 nm is largely absorbed in the epidermis, whereas that >300 nm is mostly transmitted to the dermis after variable epidermal melanin absorption. Children vary in susceptibility to UV radiation, depending on their skin type (i.e., its amount of pigment; Table 656-1).

ACUTE SUNBURN REACTION
The most common photosensitive reaction seen in children is acute sunburn. Sunburn is caused mainly by UVB radiation. Sunlight contains many times more UVA than UVB radiation, but UVA must be encountered in much larger quantities than UVB radiation to produce sunburn. Immediate pigment darkening is caused by UVA radiation–induced photooxidative darkening of existing melanin and its transfer from melanocytes to keratinocytes. This effect generally lasts for a few hours and is not photoprotective. UVB-induced effects appear 6-12 hr after initial exposure and reach a peak in 24 hr. Effects include redness, tenderness, edema, and blistering (Fig. 656-1). Severe sunburn induces systemic symptoms of fever, nausea, and headache. Reactive oxidation species generated by UVB induce keratinocyte

Table 656-1  Sun-Reactive Skin Types

<table>
<thead>
<tr>
<th>FITZPATRICK SKIN TYPE</th>
<th>SUNBURN, TANNING HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Always burns easily, no tanning</td>
</tr>
<tr>
<td>II</td>
<td>Usually burns, minimal tanning</td>
</tr>
<tr>
<td>III</td>
<td>Sometimes burns, gradual light brown tan</td>
</tr>
<tr>
<td>IV</td>
<td>Minimal to no burning, always tans</td>
</tr>
<tr>
<td>V</td>
<td>Rarely burns, tans profusely dark brown</td>
</tr>
<tr>
<td>VI</td>
<td>Never burns, pigmented black</td>
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</table>

Figure 656-1 Sunburn. Well-demarcated, severe erythema.
membrane damage and are involved in the pathogenesis of sunburn. A portion of the vasodilation seen in UVB-induced erythema is mediated by prostaglandins E₂, E₃, and F₂α. Other inflammatory cytokines induced by UVB include interleukins 1, 6, and 8, and tumor necrosis factor-α. Acute sunburn is a self-limited condition that resolves within 1 wk with desquamation and without scarring. Delayed melanogenesis as a result of UVB radiation begins in 2-3 days and lasts several days to a few weeks. Manufacture of new melanin in melanocytes, transfer of melanin from melanocytes to keratinocytes, increase in size and arborization of melanocytes, and activation of quiescent melanocytes produce delayed melanogenesis. This effect reduces skin sensitivity to development of UV-induced erythema. The amount of protection afforded depends on the skin type of the patient. Additional effects and possible complications of sun exposure include increased thickness of the stratum corneum, recurrence or exacerbation of herpes simplex labials, lupus erythematosus, and many other conditions (Table 656-2).

Acute sunburn should be managed conservatively with cool compresses, aloe vera products, and calamine lotion. Oral analgesics such as ibuprofen and acetaminophen may decrease pain. Topical corticosteroids are only helpful in the acute phase and generally should not be used to treat sunburn once peak erythema has been reached. Topical anesthetics are relatively ineffective and potentially hazardous because of their propensity to cause contact dermatitis. A bland emollient is effective in the desquamative phase.

The long-term sequelae of chronic and intense sun exposure are not often seen in children, but most individuals receive >50% of their lifetime UV dose by age 20 yr; therefore, pediatricians have a pivotal role in educating patients and their parents about the harmful effects, potential malignancy risks, and irreversible skin damage that result from prolonged exposure to the sun and tanning lights. Premature aging, senile elastosis, actinic keratoses, squamous and basal cell carcinomas, and melanomas all occur with greater frequency in sun-damaged skin. In particular, blistering sunburns in childhood and adolescence significantly increase the risk for development of malignant melanoma.

Sun protection is best achieved by sun avoidance, which includes minimizing time in the midday sun (10 AM to 3 PM), staying in the shade, and wearing protective clothing including wide-brimmed hats. Protection is enhanced by a wide variety of sunscreen agents. Physical sunscreens (zinc oxide, titanium dioxide) block UV light, whereas chemical sunscreens (para-aminobenzoic acid [PABA], PABA esters, salicylates, benzophenones, avobenzene, cinnamates, ecamsule) absorb damaging radiation. Most chemical sunscreens are effective for only UVB wavelengths but benzophenones and avobenzene provide protection in both the UVA and UVB ranges; ecamsule is a UV A sunscreen. Stabilizers such as octocrylene and diethyl 2,6-naphthalate increase the time of function of the chemical sunscreens. “Broad-spectrum” sunscreens are combination products that absorb both UVA and UVB, and families should be advised to use products labeled as “broad spectrum” with a sun protective factor (SPF) of at least 30, reapply liberally at least every 2 hr while outdoors, and reapply after swimming. Infants younger than 6 mo of age should not be exposed to direct sunlight but may have SPF 15 physical sunscreens applied to small areas of skin if sunlight avoidance is not possible. SPF is defined as the minimal dose of sunlight required to produce cutaneous erythema after application of a sunscreen, divided by the dose required with no use of sunscreen. SPF applies only to UVB protection; there is no associated rating for UVA protection in the United States aside from the “broad spectrum” designation.

PHOTOSENSITIVE REACTIONS

Photosensitizers in combination with a particular wavelength of light (typically UVA) cause dermatitis that can be classified as phototoxic or photoallergic reactions. Contact of the skin with the photosensitizer may occur externally, internally by enteral or parenteral administration, or through host synthesis of photosensitizers in response to an administered drug.

Photoallergic reactions occur in only a small percentage of persons exposed to photosensitizers and light and require a time interval for sensitization to take place. Thereafter, dermatitis appears within 24 hr of reexposure to the photosensitizer and light. Photoallergic dermatitis is a T-cell–mediated delayed hypersensitivity reaction in which the drug, acting as a hapten, may combine with a skin protein to form the antigenic substance. Photoallergic reactions vary in morphology and may occur on partially covered and on light–exposed skin. Table 656-2 lists some of the important classes of drugs and chemicals responsible for photosensitivity reactions. The most common photoallergens are chemicals present in sunscreens.

Phototoxic reactions occur in all individuals who accumulate adequate amounts of a photosensitizing drug or chemical within the skin. UV radiation excites the agent to a state capable of causing cell or tissue damage through reactive oxygen species formation. Prior sensitization is not required. Dermatitis develops within hours after exposure to radiation in the range of 285-450 nm. The eruption is confined to light-exposed areas and often resembles exaggerated sunburn, but it may be urticarial or bullous. It results in postinflammatory hyperpigmentation. All the drugs that cause photoallergic reactions may also cause a phototoxic dermatitis if given in sufficiently high doses. Several

<table>
<thead>
<tr>
<th>Table 656-2</th>
<th>Cutaneous Reactions to Sunlight</th>
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<tr>
<td><strong>SUNBURN</strong></td>
<td>Photoactive drug eruptions:</td>
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<td></td>
<td>• Systemic drugs include tetracyclines, psoralens, chlorothiazides, sulfonamides, barbiturates, griseofulvin, thiazines, quinidine, phenothiazines.</td>
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<td>• Topical agents include coal tar derivatives, psoralens, halogenated salicylanilides (soaps), perfumes oils (e.g., oil of bergamot), sunscreens (e.g., para-aminobenzoic acid [PABA], cinnamates, benzophenones).</td>
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<tr>
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<td>Phototoxic drug eruptions:</td>
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<td>• Systemic agents include nalidixic acid, furosemide, nonsteroidal antiinflammatory agents (naproxen, piroxicam), and high doses of agents causing photoallergic eruptions.</td>
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<tr>
<td></td>
<td>• Topical agents include 5-fluorouracil, furacoumarins (e.g., lime, lemon, carrot, celery, dill, parsnip, parsley), and high doses of agents causing phototoxic eruptions.</td>
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<td>Genetic disorders with photosensitivity:</td>
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<td>• Xeroderma pigmentosum</td>
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<td>• Bloom syndrome</td>
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<td>• Cockayne syndrome</td>
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<td>• Rothmund-Thomson syndrome</td>
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<td>Inborn errors of metabolism:</td>
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<td>• Porphyrias, protoporphyria</td>
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<td>• Hartnup disease and pellagra</td>
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<td>Infectious diseases associated with photosensitivity:</td>
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<td></td>
<td>• Recurrent herpes simplex infection</td>
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<td>• Viral exanthems (accentuated photodistribution; e.g., varicella)</td>
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<td>Skin disease exacerbated or precipitated by light:</td>
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<td>• Lupus erythematosus including neonatal</td>
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<td>• Psoriasis</td>
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<td>• Atopic dermatitis</td>
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<td>• Hailey-Hailey disease</td>
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<td>Deficient protection because of a lack of pigment:</td>
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<td>• Oculocutaneous albinism</td>
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additional drugs and contactants cause phototoxic reactions (see Table 656-2). Differentiating contact phototoxicity from contact dermatitis caused by poison ivy or poison oak may be difficult, but itching is prominent in contact dermatitis while burning is more prominent in photodermatitis. Postinflammatory hyperpigmentation develops rapidly and can be the presenting sign. Contact with furanocoumarin-containing plants causes a disorder called phytophotodermatitis. The most common phytophotodermatitis seen in children is caused by lime juice, which presents as hyperpigmentation in streaky patterns on sun-exposed skin consistent with dripping juice or handprints.

Diagnosis of photosensitive reactions caused by drugs or chemicals relies on a high index of suspicion, an appreciation of the distribution pattern of the eruption, and a history of application or ingestion of a known photosensitizing agent. Phototesting and photopatch testing are also helpful when available. First-line treatment for both photoallergy and phototoxicity consists of discontinuation of the offending agent and good sun protection practices, including avoidance of sun exposure. Photoallergic reactions are treated similarly to contact dermatitis, with a topical corticosteroid to alleviate pruritus when necessary. Severe reactions may necessitate a 2-3 wk course of systemic corticosteroid therapy. Phototoxic reactions are treated similarly to sunburn, with comfort measures such as cool compresses, emollients, and oral analgesics.

**PORPHYRIAS**

See Chapter 91.

Porphyrias are acquired or inborn disorders due to abnormalities of specific enzyme mutations in the heme biosynthetic pathway. Some have childhood photosensitivity as a consistent feature. The pathogenesis of photosensitivity in porphyria relates to deposition of excess porphyrins in the skin; UV radiation excites these molecules, causing cell and tissue damage via generation of reactive oxygen species. Signs and symptoms may be negligible during the winter, when sun exposure is minimal.

Congenital erythropoietic porphyria (Günther disease) is a rare autosomal recessive disorder affecting the enzyme uroporphyrinogen III synthase. It may cause hydrops fetalis, but more typically manifests in the 1st few mo of life as hemolytic anemia and exquisite sensitivity to light, which may induce repeated severe bullous eruptions that result in mutilating scars (Fig. 656-2). Hyperpigmentation, hyperkeratosis, vesiculation, and fragility of skin as well as various nail changes develop in light-exposed areas. Light therapy for an affected neonate presenting with jaundice may inadvertently induce skin manifestations, Hirsutism in areas of mild involvement, scarring alopecia in severely affected areas, pink to red urine, brown teeth (erythrodontia), splenomegaly, and corneal ulceration are additional characteristic manifestations.

Laboratory findings include uroporphyrin I and coproporphyrin I in urine, plasma, and erythrocytes, and coproporphyrin I in feces. Teeth and urine from affected patients fluoresce reddish pink under a Wood lamp as a result of the presence of porphyrins. Skin findings for hepatoerythropoietic porphyria closely resemble those seen in congenital erythropoietic porphyria; this extremely rare disorder presents in early childhood and is discussed in greater depth in Chapter 91.

Erythropoietic protoporphyria may be autosomal dominant, autosomal recessive, or X-linked and most commonly involves the enzyme ferrochelatase (FECH). Symptoms develop in early childhood and manifest as intense pain, tingling, or pruritus within 30 minutes of sun exposure, followed by erythema, edema, urticaria, or mild systemic symptoms; these acute manifestations resolve completely within days. The absence of blistering distinguishes erythropoietic protoporphyria from the other cutaneous porphyrias. Nail changes consist of opacification of the nail plate, onycholysis, pain, and tenderness. Recurrent sun exposure produces a subtle chronic eczematous dermatitis with thickened, lichenified skin, especially over the finger joints (Fig. 656-3A), as well as mild facial scarring (Fig. 656-3B). Pigmentation, hypertrichosis, skin fragility, and mutilation are not seen. Gallstones develop frequently; however, severe liver disease occurs in <5% of patients. Protoporphyria is detected in plasma, erythrocytes, and feces.

The wavelengths of light mainly responsible for eliciting cutaneous reactions in porphyria are in the region of 400 nm (UVA light). Window glass, including that in automobiles, transmits wavelengths >320 nm and is not protective, and fluorescent indoor lights may be pathogenic. Patients must avoid direct sunlight, wear protective clothing, and use a sunscreen agent that effectively blocks UVA light. Oral beta-carotene also provides some photoprotective benefit. Cutaneous porphyria symptoms are typically constant throughout life, and secondary bacterial infections commonly complicate disease course. Cutaneous porphyrias do not appear to increase risk for skin malignancies. Diagnostic and treatment recommendations for congenital erythropoietic porphyria and erythropoietic protoporphyria are outlined in Chapter 91.

![Figure 656-2](image1.png)  
**Figure 656-2** Crusted ulcerations in an infant with congenital erythropoietic porphyria.

![Figure 656-3](image2.png)  
**Figure 656-3** Erythropoietic protoporphyria. A, Erythematous thickening over the metacarpal phalangeal joints. B, Linear crusts and scarring.
**COLOID MILIUM**

Colloid milium is a rare, asymptomatic disorder that occurs on the face (nose, upper lip, upper cheeks) and may extend to the dorsum of the hands and the neck as a profuse eruption of tiny, ivory to yellow, firm, grouped papules. Lesions appear before puberty on otherwise normal skin, unlike the adult variant that develops on sun-damaged skin. Onset may follow an acute sunburn or long-term sun exposure. Most cases reach maximal severity within 3 yr and remain unchanged thereafter, although the condition may remit spontaneously after puberty. Treatment is usually not necessary.

**HYDROA VACCINIFORME**

Hydroa vacciniforme is a vesiculobullous disorder with unclear etiology, although chronic or latent Epstein-Barr virus infections or lymphoproliferative disorders have been implicated. It begins in early childhood and may remit at puberty, with peak incidence in the spring and summer. Erythematous, pruritic wheals develop on sun-exposed skin (Fig. 656-4) within 5-10 minutes of sun exposure and fade within hours of sun exposure over the ears, nose, lips, cheeks, and dorsal surfaces of the hands and forearms. Lesions progress to stinging tender papules and hemorrhagic vesicles and bullae, resembling chickenpox. They become umbilicated, ulcerated, and crusted, eventually healing with pitted scars and telangiectasias. Associated features are rare but include fever, malaise, hypersensitivity to mosquito bites, conjunctivitis, and other ocular symptoms. This eruption should be distinguished from erythropoietic protoporphyria, which rarely shows vesicles. Typical lesions have been reproduced with repeated doses of UVA or UVB light. First-line treatment includes sun avoidance, broad-spectrum sunscreens, and other sun-protective habits. Other potential therapies include mid-potency topical corticosteroids for inflamed lesions, low-dose courses of narrow-band UVB (NB-UVB) therapy, beta-carotene, hydroxychloroquine, or antiviral agents such as acyclovir.

**SOLAR URTICARIA**

Solar urticaria is a rare disorder induced by UV or visible irradiation. The disorder is mediated by immunoglobulin E antibodies to either an abnormal photoaillergen present only in affected patients (type I) or a normal photoaillergen ordinarily present in skin (type II), leading to mast cell degranulation and histamine release. Classic urticarial lesions consisting of erythematous pruritic wheals develop on sun-exposed skin (Fig. 656-4) within 5-10 minutes of sun exposure and fade within 24 hr. Severe reactions involving large areas of skin may lead to systemic symptoms or anaphylaxis. Diagnosis is achieved by history alone or with phototesting. First-line treatment is an oral H1 antihistamine, temic symptoms or anaphylaxis. Diagnosis is achieved by history alone and provocative phototesting, as well as skin biopsy showing epidermal spongiosis and superficial and deep lymphocytic infiltrate, aid in diagnosis. Treatment is aimed at prevention with sun avoidance, protective clothing, and broad-spectrum sunscreens. Topical corticosteroids (low-potency for facial lesions, high-potency for lesions elsewhere) can be used for mild eruptions. Second-line therapy possibilities include oral or topical corticosteroids, photodesensitization using NB-UVB, omalizumab, or intravenous immunoglobulin.

**POLYMORPHOUS LIGHT ERUPTION**

Polymorphous light eruption (PMLE) is a common photosensitivity reaction that develops most commonly in females. The first eruption typically appears in the spring after the first episode of prolonged sun exposure of the season. Onset of the eruption is delayed by hours to days after sun exposure and lasts for days to sometimes weeks. PMLE usually resolves with increased sun exposure throughout the spring and summer. Areas of involvement tend to be symmetric and are characteristic for a given patient, including some but not all of the exposed or lightly covered skin on the face, neck, upper chest, and distal extremities. Lesions have various morphologies but most commonly are pruritic, 2-5 mm, grouped, erythematous papules or papules; lesions are nonscarring. A PMLE variant known as juvenile spring eruption characteristically occurs on affected boys’ ears each spring, while pinpoint popular PMLE is a variant characterized by pinpoint-sized lesions occurring in darker-skinned individuals. Most PMLE cases involve sensitivity to UVA radiation, although some are UVB induced. PMLE most likely results from a delayed-type hypersensitivity reaction to a photoinduced antigen within the skin, with individuals having a genetic predisposition. Provocative phototesting, as well as skin biopsy (showing epidermal spongiosis and superficial and deep lymphocytic infiltrate), aid in diagnosis. Treatment is aimed at prevention with sun avoidance, protective clothing, and broad-spectrum sunscreens. Topical corticosteroids (low-potency for facial lesions, high-potency for lesions elsewhere) can be used for mild eruptions. Second-line approaches include prophylactic NB-UVB phototherapy or hydroxychloroquine in early spring and short course systemic glucocorticoids for severe flares.

**ACTINIC PRURIGO**

Actinic prurigo, often classified as a variant of PMLE, is a chronic familial photodermatitis inherited as an autosomal dominant trait seen most commonly in Native Americans of North and South America. Human leukocyte antigen (HLA) DRB1*0407 (60-70%) and HLA DRB1*0401 (20%) are strongly associated with actinic prurigo. Most patients are female and are sensitive to UVA radiation. The first episode generally occurs in early childhood, several hr to 2 days after intense sun exposure. The papulonodular lesions are intensely pruritic, erythematous, and crusted. Areas of predilection include the face (Fig. 656-5), lower lip, distal extremities, and, in severe cases, buttocks. Facial lesions may heal with minute pitted or linear scarring. Lesions often become chronic, without periods of total clearing, merging into
eczematous plaques that become lichenified and occasionally secondarily infected. Associated features that distinguish this disorder from other photoeruptions and atopic dermatitis include chelitis, conjunctivitis, and traumatic alopecia of the outer half of the eyebrows. Actinic prurigo is a chronic condition that generally persists into adult life, although it may improve spontaneously in the late teenage years. Sun avoidance, protective clothing, and broad-spectrum sunscreens may be helpful in preventing the eruption. Mid- to high-potency topical corticosteroids and antihistamines palliate the pruritus and inflammation. Severe acute eruptions may require oral glucocorticoids. Treatment with NB-UVB beginning in springtime has shown improved tolerance of sunlight during summer months; however, it may induce symptoms in some patients. Thalidomide 50-100 mg/day is very effective, but its use is limited by toxicity, especially severe birth defects when taken by pregnant females.

**COCKAYNE SYNDROME**

Cockayne syndrome is a rare autosomal recessive disorder. Onset occurs at 1 year of age and is characterized by facial erythema in a butterfly distribution after sun exposure. Later characteristics include loss of adipose tissue and development of thin, atrophic, hyperpigmented skin, particularly over the face. Associated features include dwarfism; microcephaly; mental retardation; progressive dementia; distinct facies (aged look, pinched nose, sunken eyes, large protuberant ears); long limbs; disproportionately large hands and feet; cool and cyanotic extremities; carious teeth; unsteady gait with tremor; limitation of joint mobility; progressive deafness; cataracts; retinal degeneration; optic atrophy; decreased sweating and tearing; and premature graying of the hair. Complications include diabetes and hepatic or renal impairment. Diffuse extensive demyelination of the peripheral and central nervous systems ensues, and patients generally die of ath-eromatous vascular disease or infections (especially pneumonia) before the 3rd decade. There are 2 types of Cockayne syndrome. Type I (CSA gene) is less severe than type II (CSB gene). Patients may have xeroderma pigmentosum–Cockayne syndrome overlap, which is pheno-typically more like Cockayne syndrome. Photosensitivity in Cockayne syndrome is a result of deficient nucleotide excision repair of UV-induced damage, specifically within actively transcribing regions of DNA (transcription-coupled DNA repair). The etiology of neurologic and other associated features remains unclear; however, evidence points toward a mitochondriopathy. The syndrome is distinguished from progeria (see Chapter 90) by the presence of photosensitivity and ocular abnormalities and from xeroderma pigmentosum by the fact that patients with Cockayne syndrome do not develop skin cancers. Diagnosis is accomplished by genetic testing and performing various tests on cultured fibroblasts. The mainstay of treatment for the photosensitivity of Cockayne syndrome is strict sunlight avoidance and protective measures.

**XERODERMA PIGMENTOSUM**

Xeroderma pigmentosum is a rare autosomal recessive disorder that results from a defect in nucleotide excision repair. Eight genetic groups have been recognized on the basis of each group’s separate defect in ability to repair (xeroderma pigmentosum A through G) or replicate (xeroderma pigmentosum V [variant]) damaged DNA. The wavelength of light that induces the DNA damage ranges from 280-340 nm. Skin changes are first noted during infancy or early childhood in sun-exposed areas though lesions may occur at other sites, including the scalp. The skin lesions consist of erythema, scaling, bullae, crusting, ephelides (freckles), telangiectasia, keratoses (Fig. 656-6), basal and squamous cell carcinomas, and malignant melanomas. Interestingly, although most patients experience exaggerated acute sunburn reactions following minimal UV exposure, up to half of affected patients do not and instead develop progressive freckling. This difference in presentation depends on genetic subtype. Ocular manifestations include photophobia, lacrimation, blepharitis, symblepharon, keratitis, corneal opacities, tumors of the lids, and possible eventual blindness. Neurologic abnormalities such as cognitive deterio-ration and sensorineural deafness develop in approximately 20% of patients.

This disease is a serious mutilating disorder, and the life span of an affected patient is often brief. Affected families should have genetic counseling. Xeroderma pigmentosum is detectable in cells cultured from amniotic fluid or DNA analysis of chorionic villous samples. Cultured skin fibroblast tests and genetic testing after birth also confirm diagnosis. Affected children should be totally protected from sun exposure; protective clothing, sunglasses, and opaque broad-spectrum sunscreens should be used even for mildly affected children. Light from unshielded fluorescent bulbs and sunlight passing through glass windows (including vehicle windows) are also harmful, thus applied window films are recommended. Early detection and removal of malignancies is mandatory, and oral isotretinoin may be used to prevent nonmelanoma skin cancers. There is crossover between several subtypes of xeroderma pigmentosum and both Cockayne syndrome and trichothiodystrophy.

**ROTHMUND-THOMSON SYNDROME**

Rothmund-Thomson syndrome is also known as poikiloderma congenitale because of the striking skin changes (Fig. 656-7). It is inherited as an autosomal recessive trait. Mutations in the RECQL4 gene, which encodes a DNA helicase involved in repair and replication of DNA and
telomeres, are found in approximately 65% of patients. The other mutations causing Rothmund-Thomson syndrome are unknown. Skin changes are noted as early as 3 mo of age and begin on the face. Plaques of erythema and edema appear in a butterfly distribution, as well as on the forehead, ears, neck, dorsal portions of the hands, extensor surfaces of the arms, and buttocks. These are replaced gradually by poikilodermia (reticulated, atrophic, hyperpigmented and hypopigmented telangiectatic patches or plaques). Palmoplantar hyperkeratosis develops in one-third of patients. Light sensitivity is present in many cases, and exposure to the sun may provoke formation of bullae. Areas of involvement, however, are not strictly photodistributed. Short stature; small hands and feet; sparse eyebrows, eyelashes, and pubic and axillary hair, and sparse, fine, prematurely gray scalp hair or alopecia; dystrophic nails; various tooth and skeletal abnormalities; and hypogonadalism are common. Cataracts may also occur at an early age. Most patients have normal mental development. Keratoses and later squamous cell carcinomas may develop on exposed skin. The most worrisome association is that with osteosarcoma, which occurs only in those patients with Rothmund-Thomson syndrome and RECQL4 mutations. Genetic testing aids diagnosis. Management of dermatologic findings begins with sun avoidance and protection behaviors, and telangiectatic lesions have been shown to respond to pulsed dye laser therapy. In the absence of malignancy, life expectancy is normal.

**BLOOM SYNDROME**

Bloom syndrome is inherited in an autosomal recessive manner, most commonly in the Ashkenazi Jewish population. It is caused by a mutation in the *BLM/RECQL3* gene, encoding a DNA helicase. Patients are sensitive to UV radiation, with increased rates of chromosomal breaks and sister chromatid exchanges. Erythema and telangiectasia develop during infancy in a butterfly distribution on the face after exposure to sunlight. A bullous eruption on the lips and telangiectatic erythema on the hands and forearms may develop. Café-au-lait spots and hypopigmented macules may be present. Intrauterine growth deficiency developing into short stature and a distinctive facies consisting of a prominent nose and ears and a small, narrow face are generally found.Intellect is average to low average. Immunodeficiency is seen in all patients, manifesting as recurrent ear and pulmonary infections. Gastrointestinal malabsorption, gastroesophageal reflux, and hypogonadism are common. Affected children have an unusual tendency to develop both solid tumors (especially of the skin) and lymphoreticular malignancies, which often result in death during childhood or early adulthood. Sister chromatid exchange analysis is generally performed to confirm diagnosis. The only effective measures to reduce skin disease are sun protection and avoidance.

**HARTNUP DISEASE**

See Chapter 85.5.

Hartnup disease is a rare inborn error of metabolism with autosomal recessive inheritance. Neutral amino acids, including tryptophan, are not transported across the brush border epithelium of the intestine and kidneys due to mutation of the *SLC6A19* gene encoding the transporter. This results in deficiency of nicotinamide synthesis and causes a photo-induced *pellagra-like syndrome*. The urine contains increased amounts of monoamine monokarboxylic amino acids, distinguishing Hartnup disease from dietary pellagra. Cutaneous signs, which precede neurologic manifestations, initially develop during the early months of life. An eczematous, occasionally vesiculobullous, eruption occurs on the face and extremities in a glove-and-stocking photodistribution. Hyperpigmentation and hyperkeratosis may supervene and are intensified by further exposure to sunlight. Episodic flares may be precipitated by febrile illness, sun exposure, emotional stress, and poor nutrition. In most cases, mental development is normal, but some patients display emotional instability and episodic cerebellar ataxia. Neurologic symptoms are fully reversible. Administration of nicotinamide and protection from sunlight results in improvement of both cutaneous and neurologic manifestations.

*Bibliography is available at Expert Consult.*
Bibliography
ETIOLOGY/PATHOGENESIS
Psoriasis is an inflammatory autoimmune-related disease characterized by inflammation and keratinocyte proliferation. Within the dermis, dendritic cells are activated by self-antigens and release cytokines such as interferon-γ, tumor necrosis factor, and interleukin (IL)-12, IL-17, IL-22, and IL-23, which recruit T cells. Once activated, the T cells release cytokines that induce proliferation and abnormal differentiation of epidermal keratinocytes; in turn, more cytokines are produced to perpetuate the cycle. Psoriasis has a complex multifactorial genetic basis. The major psoriasis-susceptibility gene \((PSORS1)\) is human leukocyte antigen (HLA)-CW\(^*\)0602, encoding a class I major histocompatibility complex protein involved in recognition of self-antigens. Numerous other psoriasis susceptibility genes have been identified. Factors contributing to disease onset/flare in some patients include bacterial and viral infections, trauma, physical or emotional stress, tobacco use/secondhand exposure, and certain medications. There is an association between psoriasis and childhood obesity worldwide.

CLINICAL MANIFESTATIONS
This common, chronic skin disorder is first evident within the 1st 2 decades of life for approximately 30% of affected individuals. Plaque psoriasis, the most common (>80%) subtype, is characterized by erythematous papules that coalesce to form plaques with sharply demarcated, irregular borders. If they are unaltered by treatment, a thick silvery or yellow-white scale (resembling mica) develops (Fig. 657-1A). Removal of the scale may result in pinpoint bleeding (Auspitz sign). The Koebner phenomenon, in which new lesions appear at sites of trauma, is a valuable diagnostic feature. Lesions may occur anywhere, but preferred sites are the scalp, knees, elbows, umbilicus, superior intergluteal fold, genitals, and ear canal. Nail involvement, a valuable diagnostic sign, is characterized by pitting of the nail plate, detachment of the plate (onycholysis), yellowish-brown subungual discoloration, and accumulation of subungual debris (Fig. 657-1B). Plaques are generally asymptomatic; however, pruritus is more common in children than adults.

Guttate psoriasis, a variant that occurs predominantly in children, is characterized by an acute eruption of many oval or round papules smaller than 1.5 cm that are morphologically identical to the larger plaques of psoriasis (see Fig. 657-1C). Sites of predilection are the trunk, face, and proximal portions of the limbs. The onset usually follows a streptococcal infection such as pharyngitis; thus, throat culture and serologic titers should be obtained. Guttate psoriasis has also been observed after perianal streptococcal infection, viral infections, sunburn, and withdrawal of systemic corticosteroid therapy or tumor necrosis factor (TNF)-\(\alpha\) inhibitors. Clinical course ranges from spontaneous resolution to chronic disease.

Pustular psoriasis is a multisystem autoinflammatory disease characterized by recurrent episodes with the sudden onset of fever, malaise, extracutaneous organ involvement, and a diffuse erythematous-pustular exanthema. It may be associated with plaque psoriasis in some patients; unregulated cytokine production as a result of mutations in the IL-36Ra gene is implicated. Psoriasis is rare in infants but may be severe and recalcitrant and may pose a diagnostic problem. Psoriatic diaper rash is a common presentation in children younger than 2 yr old. Other rare forms
include psoriatic erythroderma, localized or generalized pustular psoriasis, linear psoriasis, palmoplantar psoriasis, and inverse psoriasis (occurring in intertriginous areas).

**DIFFERENTIAL DIAGNOSIS**
Psoriasis is a clinical diagnosis. The differential diagnosis of plaque-type psoriasis includes nummular dermatitis, tinea corporis, seborrheic dermatitis, postinfectious arthritis syndromes, and pityriasis rubra pilaris. Scalp lesions may be confused with seborrheic dermatitis, atopic dermatitis, or tinea capitis. Diaper area psoriasis may mimic seborrheic dermatitis, eczematous diaper dermatitis, perianal streptococcal disease, or candidiasis. Guttate psoriasis can be confused with viral exanthems, secondary syphilis, pityriasis rosea, and pityriasis lichenoides chronica (PLC). Nail psoriasis must be differentiated from onychomycosis, lichen planus, and other causes of onychodystrophy.

**PATHOLOGY**
When the diagnosis is in doubt, histopathologic examination of an untreated lesion can be helpful. Characteristic changes of psoriasis include parakeratosis, acanthosis, elongated rete ridges, neutrophilic infiltrate in the epidermis sometimes forming microabscesses, dilated dermal blood vessels, and lymphocytic infiltrate in the dermis.

**TREATMENT**
The therapeutic approach varies with the age of the child, type of psoriasis, sites of involvement, and extent of the disease. Physical and chemical trauma to the skin should be avoided as much as possible to prevent Koebner response lesions. The treatment of psoriasis should be viewed as a 4-tier process.

The first tier is topical therapy. The first-line topical agents for lesions on the body are emollients, vitamin D analogs (calcipotriene or calcitriol, although calcitriol is less irritating for children), and mid- to high-potency corticosteroids (see Chapter 646). A proprietary formulation containing both calcipotriene and betamethasone dipropionate (a high-potency topical corticosteroid) exists in ointment and solution forms. The preparation that is least potent but effective should be applied twice a day. Second-line topical options for lesions on the body include retinoids (tazarotene), tar preparations, anthralin, and keratolytics (salicylic acid or urea). Facial or intertriginous lesions may be treated with low-potency topical corticosteroids, and/or topical vitamin D analogs or calcineurin inhibitors as corticosteroid-sparing agents. For scalp lesions, applications of a phenol and saline solution (e.g., Baker Cummins P & S liquid) followed by a tar shampoo are effective in the removal of scales. A high- to superpotency corticosteroid in a foam, solution, or lotion base may be applied when the scaling is diminished. Nail lesions are difficult to treat topically; the first-line approach is a high-potency topical corticosteroid to the proximal nail fold.

The second tier of therapy is phototherapy. Narrow-band UVB (311 nm; NB-UVB) irradiation is the primary form of UVB therapy used in childhood. If available, phototherapy should be used alone or with tar (“Goeckerman treatment”) for older children with extensive disease in whom topical therapy alone has failed. Excimer (308 nm) laser UVB irradiation may be used for localized treatment-resistant plaques. Exposure to natural sunlight is often effective for less-severe psoriasis.

The third tier is systemic therapy, required rarely for children with severe and generalized psoriasis. Methotrexate (0.2-0.7 mg/kg/wk) is the first-line systemic agent for children; other options include oral...
Pityriasis lichenoides encompasses a disease spectrum ranging from pityriasis lichenoides chronica (PLC) to pityriasis lichenoides et varioliformis acuta (PLEVA; Mucha-Habermann disease). The designation of pityriasis lichenoides as acute or chronic refers to the morphologic appearance of the lesions rather than to the duration of the disease. No correlation is found between the type of lesion at the onset of the eruption and the duration of the disease. Many patients have both acute and chronic lesions simultaneously, and transition of lesions from 1 form into another occurs occasionally. Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare subtype of PLEVA that is more severe and potentially life-threatening.

**ETIOLOGY(PATHOGENESIS**

Two main theories exist for the etiology of pityriasis lichenoides. The first is that it arises in a genetically susceptible individual as a hyperreactive reaction to an infection. The second is that it represents a monoclonal T-cell lymphocytic proliferation on the pathway to cutaneous T-cell dyscrasia.

**CLINICAL MANIFESTATIONS**

Pityriasis lichenoides most commonly manifests in the 2nd and 3rd decades of life; 30% of cases manifest before age 20 yr. The overall eruption persists for months to years with a tendency to eventually remit.

PLC manifests gradually as generalized, multiple, 3-5 mm, brown-red papules that are covered by a fine grayish scale (Fig. 657-2). Lesions may be asymptomatic or may cause minimal pruritus and occasionally become vesicular, hemorrhagic, crusted, or superinfected. Individual papules become flat and brownish in 2-6 wk, ultimately leaving a hyperpigmented or hypopigmented macule. Scarring is unusual. Various stages of lesions are present most commonly on the trunk and extremities and generally spare the face, palmar-plantar surfaces, scalp, and mucous membranes.

PLEVA manifests as an abrupt eruption of numerous papules that have a vesiculopustular and then a purpuric center, are covered by a dark adherent hemorrhagic or necrotic crust, and are surrounded by an erythematous halo (Fig. 657-3). Constitutional symptoms, such as fever, malaise, headache, and arthralgias, may be present for 2-3 days after the initial outbreak. Lesions are distributed diffusely on the trunk and extremities, as in PLC. Individual lesions heal within a few weeks, sometimes leaving a varioliform scar, and successive crops of papules produce the characteristic polymorphous appearance of the eruption, with lesions in various stages of evolution.

FUMHD manifests as fever and ulceronecrotic nodules up to a few centimeters in diameter, which are most common on the anterior trunk and flexor surfaces of the proximal upper extremities. Hemorrhagic bullae, mucosal ulcers, arthritis, cardiomyopathy, vasculitis, abdominal complaints, and superinfection of cutaneous lesions with *Staphylococcus aureus* may also develop. The ulceronecrotic lesions heal with hypopigmented scarring in a few weeks.

**PATHOLOGY**

PLC histologically shows a parakeratotic, thickened corneal layer; epidermal spongiosis; a superficial perivascular infiltrate of macrophages and predominantly CD8 lymphocytes that may extend into the epidermis; and small numbers of extravasated erythrocytes in the papillary dermis.
Bibliography
The histopathologic changes of PLEVA and FUMHD reflect their more-severe nature. Intercellular and intracellular edema in the epidermis may lead to degeneration of keratinocytes. A dense perivascular mononuclear cell infiltrate, endothelial cell swelling, and extravasation of erythrocytes into the epidermis and dermis are additional characteristic features.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of pityriasis lichenoides includes guttate psoriasis, pityriasis rosea, drug eruptions, secondary syphilis, viral exanthems, lymphomatoid papulosis, and lichen planus. The chronicity of pityriasis lichenoides helps preclude pityriasis rosea, viral exanthems, and some drug eruptions. A skin biopsy helps distinguish pityriasis lichenoides from other entities in the differential diagnosis.

TREATMENT
In general, pityriasis lichenoides should be considered a benign condition that does not alter the health of the child. A lubricant to remove excessive scaling may be all that is necessary if the patient is asymptomatic. If treatment is required, first-line agents are oral anti-inflammatory antibiotics such as erythromycin (30-50 mg/kg/day for 2-3 mo). Topical corticosteroids (mid-potency, applied twice daily) and topical calcineurin inhibitors may help the pruritus and inflammation, but do not alter the course of the disease. Phototherapy (NB-UVB) is the second-line treatment option. Methotrexate should be reserved for severely symptomatic cases. The rare FUMHD usually requires inpatient treatment; initially, systemic corticosteroids, methotrexate, intravenous immunoglobulin, or cyclosporine may be necessary, with eventual transition to another form of treatment, as mentioned above, once the disease improves and stabilizes.

Bibliography is available at Expert Consult.

657.3 Keratosis Pilaris
Brianne Z. Dickey and Yvonne E. Chiu

Keratosis pilaris is a common papular eruption resulting from keratin plugging of hair follicles. It displays an autosomal dominant transmission with variable penetrance. Typical areas of involvement include the upper extensor surfaces of the arms and thighs, cheeks, and buttocks. The lesions may resemble gooseflesh; they are noninflammatory, scaly, follicular papules that do not coalesce. They are generally asymptomatic but may be pruritic. Irritation of the follicular plugs occasionally causes erythema surrounding the keratotic papules (Fig. 657-4). A subset of patients have keratosis pilaris associated with facial telangiectasia and ulcerethema ophryogenes, a rare cutaneous disorder characterized by inflammatory keratotic facial papules that may result in scars, atrophy, and alopecia. Because the lesions of keratosis pilaris are associated with and accentuated by dry skin, they are often more prominent during the winter. Keratosis pilaris is more frequent in patients with atopic dermatitis and is most common during childhood and early adulthood, tending to subside in the 3rd decade of life. Treatment of keratosis pilaris is optional. Measures to decrease pruritus include moisturization with a bland emollient. Regular applications of a 10-40% urea cream or an α-hydroxy acid preparation such as 12% lactic acid cream or lotion can improve the appearance of keratosis pilaris but may further contribute to pruritus and irritation. Therapy may improve the condition but does not cure it.

657.4 Lichen Spinulosus
Brianne Z. Dickey and Yvonne E. Chiu

Lichen spinulosus is an uncommon disorder that occurs principally in children and more frequently in boys. The cause is unknown. The lesions consist of sharply circumscribed irregular plaques of spiny, keratotic, follicular plugs. Plaques may occur anywhere on the body and are often distributed symmetrically on the trunk, elbows, knees, and extensor surfaces of the limbs. Although sometimes erythematous or pruritic, the lesions are usually skin colored and asymptomatic.

Treatment is usually unnecessary. For patients who regard the eruption as a cosmetic defect, urea-containing lubricants (10-40%) are often effective in flattening the projections. The plaques usually disappear spontaneously after several months or years.

657.5 Pityriasis Rosea
Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS
The cause of pityriasis rosea is unknown; a viral agent is suspected, and there is debate over the role of human herpesviruses 6, 7, and 8 in this condition. Supporting evidence for an infectious etiology is the tendency for it to occur in case clusters, although the rash itself is not contagious.

CLINICAL MANIFESTATIONS
This benign, common eruption occurs most frequently in children and young adults. Although a prodrome of fever, malaise, arthralgia, and pharyngitis may precede the eruption, children rarely complain of such symptoms. A herald patch classically precedes the generalized eruption and may occur anywhere on the body. Herald patches are generally larger than other lesions and vary from 1-10 cm in diameter; they are annular in configuration and have a raised border with fine, adherent scales. Approximately 5-10 days after the appearance of the herald patch, a widespread, symmetric eruption involving mainly the trunk and proximal limbs becomes evident (Fig. 657-5). In the inverse form of pityriasis rosea, the face, scalp, and distal limbs may be preferentially involved. Lesions may appear in crops for several days. Typical lesions are oval or round, <1 cm in diameter, slightly raised, and pink to brown. The developed lesion is covered by a fine scale, which gives the skin a crinkly appearance. Some lesions clear centrally and produce a collarette of scale that is attached only at the periphery. Papular (more common in black children), vesicular, urticarial, hemorrhagic, large annular, and mucosal lesions are unusual variants. The long axis of each lesion is usually aligned with the cutaneous cleavage lines, a feature that creates the so-called Christmas tree pattern on the back. Conformation to skin lines is often more discernible in the anterior and posterior axillary folds and supraclavicular areas. The lesions most commonly are asymptomatic but may be mildly to severely pruritic.
Bibliography
Lam J, Pope E: Pediatric pityriasis lichenoides and cutaneous T-cell lymphoma,
The Skin

Figure 657-5 Herald patch and surrounding pityriasis rosea.

Duration of the eruption varies from 2-12 wk, with self-resolution. After the eruption has resolved, postinflammatory hypopigmentation or hyperpigmentation may be pronounced, particularly in dark-skinned patients. These changes disappear in subsequent weeks to months.

DIFFERENTIAL DIAGNOSIS
The herald patch may be mistaken for tinea corporis, a pitfall that can be avoided if microscopic evaluation of a potassium hydroxide preparation of scrapings of the lesion is performed. The generalized eruption resembles a number of other diseases; secondary syphilis is the most important. Drug eruptions, viral exanthems, guttate psoriasis, PLC, and nummular dermatitis can also be confused with pityriasis rosea.

TREATMENT
Therapy is unnecessary for asymptomatic patients with pityriasis rosea. If scaling is prominent, a bland emollient may suffice. Pruritus may be suppressed by a lubricating lotion containing menthol and camphor or by an oral antihistamine for sedation, particularly at night, when itching may be troublesome. Occasionally, a mid-potency topical corticosteroid preparation may be necessary to alleviate pruritus. Exposure to natural sunlight and NB-UVB phototherapy may reduce disease duration and severity.

657.6 Pityriasis Rubra Pilaris
Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS
The cause of pityriasis rubra pilaris is unknown. Although genetic forms with autosomal dominant or recessive transmission may account for some cases in childhood, most cases are sporadic. Some studies have indicated a role for TNF-α in disease development, while other hypotheses for causal factors include abnormal vitamin A metabolism, trauma, infections, immunosuppression, and UV light exposure.

CLINICAL MANIFESTATIONS
This rare inflammatory dermatosis is known for its variability in clinical presentation and course of disease. It often has an insidious onset with diffuse scaling and erythema of the scalp, which is indistinguishable from the findings in seborrheic dermatitis, and with thick hyperkeratosis of the palms and soles (Fig. 657-6A). Lesions over the elbows and knees are also common (Fig. 657-6B), and generalized erythroderma develops in some patients. The characteristic primary lesion is a firm, dome-shaped, tiny, acuminate, pink to red papule, which has a central keratotic plug pierced by a vellus hair. Masses of these papules coalesce to form large, erethematous, sharply demarcated orange-pink plaques with overlying scale, within which islands of normal skin can be distinguished. Typical papules on the dorsum of the proximal phalanges are readily palpated. Gray plaques or papules resembling lichen planus may be found in the oral cavity. Dystrophic changes in the nails may occur and mimic those of psoriasis. Lesions are commonly pruritic. In childhood, the prognosis for eventual resolution is relatively good.

DIFFERENTIAL DIAGNOSIS
Differential diagnosis includes ichthyosis, seborrheic dermatitis, keratoderma of the palms and soles, and psoriasis.

HISTOLOGY
Skin biopsy revealing follicular plugging, epidermal acanthosis, perivascular infiltrate, checkerboard pattern of orthokeratosis and parakeratosis, and an intact granular layer may differentiate this condition from psoriasis and seborrheic dermatitis.

TREATMENT
The numerous therapeutic regimens recommended are difficult to evaluate because pityriasis rubra pilaris has a capricious course with exacerbations and remissions. Moisturization alone is useful in mild cases. Topical agents, such as mid- to high-potency corticosteroids, keratolytics (urea, salicylic acid), vitamin D analogs (calcipotriene), retinoids (tazarotene, tretinoin), and tar, are used in combination with systemic agents for widespread disease and as monotherapy for localized disease. When further treatment is necessary, oral retinoids (isotretinoin 1 mg/kg/day or acitretin 0.5 mg/kg/day) are used as first-line agents, while methotrexate is used as a second-line agent. Third-line treatment options include biologic TNF-α inhibitors, cyclosporine, azathioprine, and NB-UVB phototherapy.

Bibliography is available at Expert Consult.
Bibliography
Bibliography

657.7 Darier Disease (Keratosis Follicularis)  
Brianne Z. Dickey and Yvonne E. Chiu

**ETIOLOGY/PATHOGENESIS**  
A rare genetic disorder, Darier disease is inherited as an autosomal dominant trait and is caused by mutations in the ATP2A2 gene. This gene encodes a cellular calcium pump, and dysfunction results in loss of adhesion between epidermal cells and abnormal keratinization.

**CLINICAL MANIFESTATIONS**  
Onset usually occurs in late childhood. Typical lesions are small, firm, skin-colored, warty papules that are not always follicular in location. The lesions eventually acquire yellow, malodorous, greasy crusts and coalesce to form large, gray-brown, vegetative plaques (Fig. 657-7). The scalp, face, neck, shoulders, chest, back, axillae, limb flexures, and groin are symmetrically involved. Papules, fissures, crusts, and ulcers may appear on the mucous membranes of the lips, tongue, buccal mucosa, pharynx, larynx, and vulva. Hyperkeratosis of the palms and soles and nail dystrophy with subungual hyperkeratosis and longitudinal red and white banding are variable features. Severe pruritus, secondary infection, offensive odor, and pain may occur. Several exacerbating triggers have been identified: sweating, UV light exposure, heat, friction, and infections. Thus, Darier disease has a chronic relapsing course that usually worsens in summertime.

**HISTOLOGY**  
Histologic changes seen in Darier disease are diagnostic. Hyperkeratosis with keratin plugging, intraepidermal separation (acantholysis) with formation of suprabasal clefts, and dyskeratotic epidermal cells are characteristic features.

**DIFFERENTIAL DIAGNOSIS**  
Darier disease is most likely to be confused with seborrheic dermatitis, flat warts, or Hailey-Hailey disease.

**TREATMENT**  
Treatment is nonspecific and begins with emollients and avoidance of triggers. First-line treatment for mild/localized disease is low- to mid-potency corticosteroids; second-line is topical retinoids. Further treatment options include topical keratolytic agents (urea, lactic acid), antiseptic washes (triclosan, chlorhexidine gluconate, or bleach), or calcineurin inhibitors. More severe/generalized disease is treated with oral isotretinoin or acitretin (0.5-1.0 mg/kg/day for 3-4 mo). Secondary infections must be treated appropriately.

Bibliography is available at Expert Consult.

Figure 657-7 Papules coalescing into large plaque on the back of a patient with Darier disease.

657.8 Lichen Nitidus  
Brianne Z. Dickey and Yvonne E. Chiu

**ETIOLOGY/PATHOGENESIS**  
The etiology of lichen nitidus is unknown.

**CLINICAL MANIFESTATIONS**  
This chronic, benign, papular eruption is characterized by minute (1-2 mm), flat-topped, shiny, firm papules of uniform size. The papules are most often skin-colored but may be pink or red. In black individuals, they are usually hypopigmented (Fig. 657-8). Sites of predilection are the genitals, abdomen, chest, forearms, wrists, and inner aspects of the thighs. The lesions may be sparse or numerous and may form large plaques; careful examination usually discloses linear papules in a line of scratch (Koebner phenomenon), a valuable clue to the diagnosis because it occurs in only a few diseases. Lichen nitidus occurs in all age groups. The cause is unknown. Patients with lichen nitidus are usually asymptomatic and constitutionally well, although pruritus may be severe. The lesions may be confused with those of lichen planus, and lichen nitidus can rarely occur concurrently with lichen planus.

**DIFFERENTIAL DIAGNOSIS**  
Widespread keratosis pilaris can also be confused with lichen nitidus, but the follicular localization of the papules and the absence of Koebner phenomenon in the former distinguish them. Verruca plana (flat warts), if small and uniform in size, may occasionally resemble lichen nitidus.

**HISTOLOGY**  
Although the diagnosis can be made clinically, a biopsy is occasionally indicated. The lichen nitidus papule consists of sharply circumscribed nests of lymphocytes and histiocytes in the upper dermis enclosed by claw-like epidermal rete ridges.

**TREATMENT**  
The course of lichen nitidus spans months to years, but the lesions eventually involute completely. No treatment is necessary, but mid- to high-potency topical steroids may be used for pruritus.

Bibliography is available at Expert Consult.

Figure 657-8 Slightly hypopigmented, uniform papules of lichen nitidus.
Bibliography


Bibliography
markedly increased in skin involved with lichen planus. A genetic predisposition may exist, and other proposed triggers include metal exposure, certain medications, liver disease, vaccinations (especially hepatitis B vaccination), and infections (especially hepatitis C virus).

**CLINICAL MANIFESTATIONS**
This is a rare disorder in young children and uncommon in older ones. It is more often seen in children from the Indian subcontinent and of African-American background. The classic form of lichen planus is the most common subtype in children, often exhibiting an acute eruptive onset. The lesions erupt in an explosive fashion, much like a viral exanthem, and spread to involve most of the body surface. The primary lesion is a violaceous, sharply demarcated, polygonal papule with fine white lines (Wickham's striae) or scale on the surface. Papules may coalesce to form large plaques (Fig. 657-10). The papules are intensely pruritic, and additional papules are often induced by scratching (Koebner phenomenon) so that lines of them are detected. Sites of predilection are the flexor surfaces of the wrists, the forearms, the inner aspects of the thighs, and the ankles.

Hypertrophic, linear, bullous, atrophic, annular, follicular, erosive, ulcerative, and actinic forms of lichen planus may also occur in children. Characteristic lesions of mucous membranes consist of pinhead-size white papules that coalesce to form reticulated and lacy patterns on the buccal mucosa. Erosive ulcers are also common in the oral mucosa, and may also involve the gastrointestinal tract. Nail involvement causes nail dystrophy. The disorder may persist for months to years, but the acute eruptive form is most likely to involute permanently. Self-resolution eventually occurs. Intense hyperpigmentation frequently persists for a long time after the resolution of lesions.

**HISTOLOGY**
The histopathologic findings in lichen planus are specific, consisting of hyperkeratosis, irregular acanthosis, wedge-shaped hypergranulosis, apoptotic keratinocytes in the lower epidermis and upper dermis, and basal cell degeneration with a bandlike lymphocytic infiltrate at the epidermal-dermal junction. Pigment incontinence is frequently seen. Biopsy is indicated if the diagnosis is unclear.

**TREATMENT**
Treatment is directed at alleviation of the intense pruritus and amelioration of the skin lesions. First-line treatment with a high-potency topical corticosteroid applied twice daily is effective for localized disease on the trunk or extremities; lesions on the face and genitals may be treated with low- to mid-potency corticosteroids. Alternatives to topical steroids include topical calcineurin inhibitors or vitamin D analogs. Thick lesions may require intralesional corticosteroid injection. Oral antihistamines (hydroxyzine) are often added for the
Bibliography
pruritus. A short course of systemic glucocorticoids or phototherapy (NB-UVB) are used as second-line approaches for rare cases of widespread, intractable lesions. Other medications with efficacy include oral retinoids (acitretin), dapsone, metronidazole, griseofulvin, and methotrexate.

Bibliography is available at Expert Consult.

657.11 Porokeratosis
Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS
Porokeratosis is a disorder of epidermal keratinization. The etiology is unknown except for the disseminated actinic form, which is secondary to chronic sun exposure. Genetic susceptibility, with autosomal dominant transmission, and immunosuppression may also be involved.

CLINICAL MANIFESTATIONS
Porokeratosis is a rare, chronic, progressive disease of keratinization. The prototypical lesion is an atrophic papule or plaque with a surrounding ridge of hyperkeratosis, called cornoid lamella. Several forms have been delineated: solitary plaques, linear porokeratosis, hyperkeratotic lesions of the palms and soles, disseminated eruptive lesions, and superficial actinic porokeratosis. Classic porokeratosis of Mibelli begins in childhood and is more common in males. Sites of predilection are the limbs, face, genitals, mucous membranes, palms, and soles. The primary lesion is a small, keratotic papule that slowly enlarges peripherally so that the center becomes depressed, with the edge forming an elevated wall or collar (Fig. 657-11). The configuration of the plaque may be round, oval, or gyrate. The elevated border is split by a thin groove from which minute cornified projections protrude. The central atrophic area is yellow, gray, or tan, and sclerotic, smooth, and dry, whereas the hyperkeratotic border is a darker gray, brown, or black. Linear porokeratosis is also more common in childhood and typically follows the lines of Blaschko. The disease is slowly progressive but relatively asymptomatic; some patients experience pruritus or pain. Malignant degeneration to squamous cell carcinoma has been reported in long-standing cases.

HISTOLOGY
A skin biopsy is usually unnecessary, but will disclose the characteristic cornoid lamella (plug of stratum corneum cells with retained nuclei), which is responsible for the invariable linear ridge of the lesion. The granular layer is absent beneath the cornoid lamella.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of porokeratosis includes warts, epidermal nevi, lichen planus, granuloma annulare, tinea corporis, nummular eczema, pityriasis rosea, and elastosis perforans serpiginosa.

TREATMENT
No treatment is uniformly successful, thus therapeutic decisions depend largely on lesion size, location, symptoms, and patient preference. Most lesions are asymptomatic and do not require any intervention; however, when treatment is necessary options include pharmacologic management (topical retinoids, topical 5-fluorouracil, topical imiquimod, or oral retinoids [severe cases only]), destructive therapy (liquid nitrogen cryotherapy, electrodessication and curettage, or various lasers), and surgical removal. In general, the less-invasive topical agents should be attempted first. Good sunlight protection should also be encouraged to decrease risk of malignant transformation.

Bibliography is available at Expert Consult.

657.12 Gianotti-Crosti Syndrome
(Papular Acrodermatitis)
Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS
The pathogenesis of Gianotti-Crosti syndrome, also known as papular acrodermatitis, is unclear, but an immunologic reaction to viral infections and immunizations has been postulated. Historically, the most common associations are with Epstein-Barr virus, hepatitis B virus (primarily in countries without routine childhood vaccination programs), coxsackievirus A16, and parainfluenza virus, as well as with many childhood immunizations.

CLINICAL MANIFESTATIONS
This distinctive eruption is benign and predominantly occurs in children younger than 5 yr old about 1 wk after a viral illness. Cases are usually sporadic, but epidemics have been recorded. Skin lesions are monomorphic, firm, dusky or coppery red papules ranging in size from 1-10 mm (Fig. 657-12), although there is considerable variation in lesion appearance between patients. The papules often have the appearance of vesicles; when opened, however, no fluid is obtained. The papules sometimes become hemorrhagic. Lines of papules (Koebner phenomenon) may be noted on the extremities following minor local
Bibliography
Bibliography
Acanthosis nigricans is characterized by symmetric, hyperpigmented, velvety, hyperkeratotic plaques with exaggerated skin lines in intertriginous areas. The most common locations are the posterior neck and axillae (Fig. 657-13), but it is also seen in the inframammary areas, groin, inner thighs, and anogenital region. Prior to plaque development, patients notice a “dirty” appearance of affected skin that does not wash clean. Skin lesions remain asymptomatic unless maceration or secondary infection occurs. Acanthosis nigricans is found more commonly in African-American, Hispanic, and Native American children. The clinical severity and histopathologic features of acanthosis nigricans correlate positively with the degree of hyperinsulinism and with the degree of obesity.

HISTOLOGY
The histologic changes are those of papillomatosis and hyperkeratosis rather than acanthosis or excessive pigment formation. A mild dermal inflammatory infiltrate may be present.
Bibliography

Bibliography
DISORDERS OF CORNIFICATION
Mendelian disorders of cornification (ichthyoses) are a primary group of inherited conditions characterized clinically by patterns of scaling and histopathologically by hyperkeratosis. They are usually distinguishable on the basis of inheritance patterns, clinical features, associated defects, and histopathologic changes (Table 658-1). Much work is currently underway to better categorize the genotype-phenotype correlation of these diseases.

COLLODION BABY
Collodion baby is not a single entity but a newborn phenotype that is most often seen in babies who will eventually demonstrate lamellar ichthyosis or congenital ichthyosiform erythroderma. Less commonly, collodion babies evolve into babies with other forms of ichthyosis or Gaucher disease. A small subset become otherwise healthy babies without chronic skin disease.
Collodion babies are covered at birth by a thick, taut membrane resembling oiled parchment or collodion (Fig. 658-1), which is subsequently shed. Affected neonates have ectropion, flattening of the ears and nose, and fixation of the lips in an O-shaped configuration. Hair may be absent or may perforate the abnormal covering. The membrane cracks with initial respiratory efforts and, shortly after birth, begins to desquamate in large sheets. A high-humidity environment and application of nonocclusive lubricants facilitates shedding of the membrane. Complete shedding may take several weeks, and a new membrane may occasionally form in localized areas. Neonatal morbidity and mortality may be due to cutaneous infection, aspiration pneumonia (squamous material), hypothermia, or hypernatremic dehydration from excessive transcutaneous fluid losses as a result of increased skin permeability. The outcome is uncertain.

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<td>Various</td>
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AD, autosomal dominant; AR, autosomal recessive; FAD, fatty aldehyde.

The Skin Treatment

Scaling may be diminished by daily applications of an emollient or a lubricant containing urea (10-40%), salicylic acid, or an α-hydroxy acid such as lactic acid (5-12%).

X-Linked Ichthyosis

Etiology/Pathogenesis

X-linked ichthyosis (XLI) involves a deficiency of steroid sulfatase, which hydrolyzes cholesterol sulfate and other sulfated steroids to cholesterol. Cholesterol sulfate accumulates in the stratum corneum and plasma. In the epidermis this accumulation causes malformation of intercellular lipid layers, leading to barrier defects and delay of corneodesmosome degradation, resulting in corneocyte retention.

Clinical Manifestations

Skin peeling may be present at birth but typically begins at 3-6 mo of life. Scaling is most pronounced on the sides of the neck, lower face, preauricular areas, anterior trunk, and the limbs, particularly the legs. The elbow (Fig. 658-3) and knee flexures are generally spared but may be mildly involved. The palms and soles may be slightly thickened but are also usually spared. The condition gradually worsens in severity and extent. Keratosis pilaris is not present, and there is no increased incidence of atopy. Deep corneal opacities that do not interfere with vision develop in late childhood or adolescence and are a useful marker for the disease because they may also be present in carrier females. Some patients have larger deletions on the X chromosome that encompass neighboring genes, generating contiguous gene deletion syndromes. These include Kallmann syndrome (KAL1 gene), which consists of hypogonadotrophic hypogonadism and anosmia, X-linked chondrodysplasia punctata (ARSE gene), short stature, and ocular albinism. The rate of testicular cancer may be increased in patients with coexistent Kallmann syndrome. There is also an increased risk of attention deficit hyperactivity disorder and autism owing to a contiguous gene defect in neurexin 1.

Reduced steroid sulfatase enzyme activity can be detected in fibroblasts, keratinocytes, and leukocytes and, prenatally, in amniocytes or chorionic villus cells. In affected families, an affected male can be detected by restriction enzyme analysis of cultured chorionic villus cell DNA or amniocytes or by in situ hybridization, which identifies steroid sulfatase gene deletions prenatally in chorionic villus cells. A placental steroid sulfatase deficiency in carrier mothers may result in low urinary and serum estriol values, prolonged labor, and insensitivity of the uterus to oxytocin and prostaglandins.

Treatment

Scaling may be diminished by daily applications of an emollient or a lubricant containing urea (10-40%), salicylic acid, or an α-hydroxy acid such as lactic acid (5-12%).

COMMON ICHTHYOSSES

Ichthyosis Vulgaris

Etiology/Pathogenesis

Autosomal dominant or recessive mutations in the filaggrin gene cause ichthyosis vulgaris (IV). Filaggrin is a filament-aggregating protein that assembles the keratin filament cytoskeleton, causing collapse of the granular cells into classic flattened squamous cell shape. Mutations in filaggrin lead to absence or marked reductions in keratohyalin granules.

Clinical Manifestations

IV is the most common of the disorders of keratinization, with an incidence of 1/250 live births. Onset generally occurs in the 1st yr of life. In most cases, it is trivial, consisting only of slight roughening of the skin surface. Scaling is most prominent on the extensor aspects of the extremities, particularly the legs (Fig. 658-2). Flexural surfaces are spared, and the abdomen, neck, and face are relatively uninvolved. Keratosis pilaris, particularly on the upper arms and thighs, accentuated markings, and hyperkeratosis on the palms and soles, and atopy are relatively common. Scaling is most pronounced during the winter mo and may abate completely during warm weather. There is no accompanying disorder of hair, teeth, mucosal surfaces, or other organ systems.
emollient base and propylene glycol (40-60%) in water with occlusion overnight are alternative forms of therapy.

**AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSSES (ARCI)**

**Harlequin Ichthyosis**

**Etiology/Pathogenesis**

Harlequin ichthyosis (HI) is caused by mutations in the ABCA12 gene. Mutation in the gene leads to defective lipid transport and ABCA12 activity is required for the generation of long-chain ceramides that are essential for the development of the normal skin barrier.

**Clinical Manifestations**

At birth, markedly thickened, ridged, and cracked skin forms horny plates over the entire body, disfiguring the facial features and constricting the digits. Severe ectropion and chemosis obscure the orbits, the nose and ears are flattened, and the lips are everted and gaping. Nails and hair may be absent. Joint mobility is restricted, and the hands and feet appear fixed and ischemic. Affected neonates have respiratory difficulty, suck poorly, and are subject to severe cutaneous infection. HI used to be uniformly fatal in the neonatal period, but with the use of oral retinoids, more patients survive (~80%) beyond infancy and have severe ichthyosis usually resembling lamellar ichthyosis or nonbullous congenital ichthyosiform erythroderma as adolescents and adults. Those with a compound heterozygous genotype have a better prognosis.

**Treatment**

Initial treatment includes high fluid intake to avoid dehydration from transepidermal water loss and use of a humidified heated incubator, emulsifying ointments, careful attention to hygiene, and oral retinoids (1 mg/kg/day). Prenatal diagnosis has been accomplished by fetoscopy, fetal skin biopsy, and microscopic examination of cells from amniotic fluid.

**Lamellar Ichthyosis and Congenital Ichthyosiform Erythroderma (Nonbullous Congenital Ichthyosiform Erythroderma)**

Lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE; nonbullous congenital ichthyosiform erythroderma; non-HI ARCI) are the most common types of autosomal recessively inherited ichthyosis. Both forms are present at or shortly after birth. Most infants with these forms of ichthyosis present with erythroderma and scaling; but among collodion babies, most turn out to have one of these ichthyosis variants.

**Etiology/Pathogenesis**

Six genes have been identified that cause non-HI ARCI: TGM (the gene encoding transglutaminase), ABCA12, NIPAL4 (also known as ICHTHYIN), CYP4F22, and the lipoxygenase genes ALOX12B and ALOX13B. Transglutaminase mutations lead to abnormalities in the cornified envelope, whereas defects in ABCA12 cause abnormal lipid transport and those in CYP4F22 produce abnormal lamellar granules. The lipoxygenases are likely to play a role in epidermal barrier formation by affecting lipid metabolism.

**Clinical Manifestations**

After shedding of the collodion membrane, if present, lamellar ichthyosis evolves into large, quadrilateral, dark scales that are free at the edges and adherent at the center. Scaling is often pronounced covering the digits. Severe ectropion and chemosis obscure the orbits, the nose and ears are flattened, and the lips are everted and gaping. Nails and hair may be absent. Joint mobility is restricted, and the hands and feet appear fixed and ischemic. Affected neonates have respiratory difficulty, suck poorly, and are subject to severe cutaneous infection. HI used to be uniformly fatal in the neonatal period, but with the use of oral retinoids, more patients survive (~80%) beyond infancy and have severe ichthyosis usually resembling lamellar ichthyosis or nonbullous congenital ichthyosiform erythroderma as adolescents and adults. Those with a compound heterozygous genotype have a better prognosis.

**Treatment**

Initial treatment includes high fluid intake to avoid dehydration from transepidermal water loss and use of a humidified heated incubator, emulsifying ointments, careful attention to hygiene, and oral retinoids (1 mg/kg/day). Prenatal diagnosis has been accomplished by fetoscopy, fetal skin biopsy, and microscopic examination of cells from amniotic fluid.

**Keratinopathic Ichthyoses**

**Epidermolytic Ichthyosis**

**Etiology/Pathogenesis**

Epidermolytic ichthyosis (EI) is an autosomal dominant trait that has been shown to be due to defects in either keratin 1 or keratin 10. These
The Skin Clinical Manifestations

EKV usually manifests in the early months of life, progresses in childhood, and stabilizes in adolescence. It is characterized by two distinctive manifestations: sharply demarcated, hyperkeratotic plaques (Fig. 658-7A) and transient figurate erythema (Fig. 658-7B). The distribution is generalized but sparse; sites of predilection are the face, buttocks, axillae, and extensor surfaces of the limbs. The palms and soles may be thickened, but hair, teeth, and nails are normal.

Treatment

There are case reports that topical tazarotene gel 0.1% and oral retinoids (1 mg/kg/day) are effective for treatment of EKV.

Symmetric Progressive Erythrokeratoderma

Etiology/Pathogenesis

Symmetric progressive erythrokeratoderma is an autosomal dominant disorder caused by mutations in the gene encoding loricrin. Loricrin is a major component of the epidermal cornified cell envelope.

Clinical Manifestations

The disorder manifests in childhood as large, fixed, geographic and symmetric, fine, scaling, hyperkeratotic, erythematous plaques primarily on the extremities, buttocks, face, ankles, and wrists. The palms and soles may be thickened, but hair, teeth, and nails are normal.

Treatment

Symmetric progressive erythrokeratoderma is a very rare disorder, but reports of response to topical and oral retinoids (1 mg/kg/day) exist.

SYNDROMIC ICHTHYOSSES

Sjögren-Larsson Syndrome

Etiology/Pathogenesis

The autosomal recessive inborn error of metabolism known as Sjögren-Larsson syndrome is an abnormality of fatty alcohol oxidation that results from a deficiency of fatty aldehyde dehydrogenase (FALDH3A2), a component of the fatty alcohol–nicotinamide adenine dinucleotide oxidoreductase enzyme complex.
Clinical Manifestations
The clinical picture of Sjögren-Larsson syndrome consists of ichthyosis, cognitive impairment, and spasticity. The ichthyosis is generalized but is accentuated on the flexures and the lower abdomen and consists of erythroderma, fine scaling, larger platelike scales, and dark hyperkeratosis. The degree of scale varies markedly from patient to patient. Most individuals have palmoplantar hyperkeratosis. The skin changes may be identical to the other forms of ichthyosis, and diagnosis is often delayed until the onset of neurologic symptoms. Pruritus is severe and hypohidrosis is common. Glistening dots in the foveal area are a cardinal ophthalmologic sign. About half the patients have primary retinal degeneration. Motor and speech developmental delays are usually noted before 1 yr of age, and spastic diplegia or tetraplegia, epilepsy, and intellectual disability generally become evident in the 1st 3 yr of life. Some patients may walk with the aid of braces, but most are confined to wheelchairs. This deficiency can be demonstrated in cultured skin fibroblasts of affected patients and carriers and, prenatally, in cultured chorionic villus cells and amniocytes from affected fetuses. Elevation of urinary leukotriene B4 (LTB4) may provide an easier approach to diagnosis.

Treatment
Treatment is similar to that for the other forms of ichthyosis; 5-lipoxygenase inhibitors have been used to decrease pruritus.

Netherton Syndrome
Etiology/Pathogenesis
A rare autosomal recessive disorder, Netherton syndrome is caused by mutations in the SPINK 5 gene, which encodes a serine protease inhibitor (LEKTI).

Clinical Manifestations
Netherton syndrome is characterized by ichthyosis (usually ichthyosis linearis circumflexa but occasionally the lamellar or congenital types of ichthyosiform erythroderma), trichorrhexis invaginata and other hair shaft anomalies, and atopic diathesis. The disorder manifests at birth or in the 1st few mo of life as generalized erythema and scaling. The trunk and limbs have diffuse erythema and superimposed migratory, polycyclic, and serpiginous hyperkeratotic lesions (Fig. 658-8), some with a distinctive double-edged margin of scale. Lichenification or hyperkeratosis tends to persist in the antecubital and popliteal fossae. The face and scalp may remain erythematous and scaling. Many hair shaft deformities, most notably, trichorrhexis invaginata, have been described in most patients with Netherton syndrome.

The ichthyosis is present in the 1st 10 days of life and may be especially marked around the eyes, mouth, and perineal area. The erythroderma is often intensified after infection. Infants may suffer from failure to thrive, recurrent bacterial and candidal infections, elevated serum immunoglobulin IgE values, and marked hypernatremic dehydration. The most frequent allergic manifestations are urticaria, angioedema, atopic dermatitis, and asthma. Scalp hair is sparse and short and fractures easily (Fig. 658-9); eyebrows, eyelashes, and body hair are also abnormal. The characteristic hair abnormality can be identified with light microscopy; in the newborn, it may best be identified in eyebrow hair.

Treatment
Owing to the inflammatory nature of the skin disease, oral antihistamines and topical steroids, as used in the treatment of atopic dermatitis, are helpful for Netherton syndrome.

Refsum Syndrome
See Chapters 86.2 and 613.5.

Etiology/Pathogenesis
There are 2 types of Refsum syndrome. The classic form is autosomal recessive and caused by mutations in the PAHX gene that result in an increase in phytanic acid. The infantile forms of Refsum syndrome are also autosomal recessive and caused by mutations in the PEX1, PEX2, or PEX26 genes. These are peroxisomal abnormalities that lead to an increase in very long chain fatty acids, di- and tri-hydroxycholestanolic acid, and piperolic acid.

Clinical Manifestations
Refsum syndrome is a multisystem disorder that becomes symptomatic in the 2nd or 3rd decade of life. The ichthyosis may be generalized, is relatively mild, and resembles ichthyosis vulgaris. The ichthyosis may also be localized to the palms and soles. Chronic polynuropathy with progressive paralysis and ataxia, retinitis pigmentosa, anosmia, deafness, bony abnormalities, and electrocardiographic changes are the most characteristic features. The condition is diagnosed through lipid analysis of the blood or skin, which shows elevated phytic acid values.

The infantile form begins, as suggested by the name, early in life, and in addition to the changes seen in the classic form, affected patients have hepatomegaly, abnormal bile acid profiles, developmental delay, and cognitive impairment.
Treatment
Phytanic acid is exclusively derived from dietary chlorophyll. Life-long dietary avoidance of phytanic acid–containing produces clinical improvement in classic Refsum syndrome.

Chondrodysplasia Punctata
See Chapter 86.2.

Etiology/Pathogenesis
Chondrodysplasia punctata (CPD) is a clinically and genetically heterogeneous condition. X-linked dominant CPD, also known as Conradi-Hünermann syndrome, is the best-characterized form. There is also an X-linked recessive form caused by mutation in the ARSE gene. Rhizomelic chondrodysplasia punctata type 1 is an autosomal recessive disorder caused by mutations in the PEX7 gene, which encodes the peroxisomal type 2 targeting signal (PTS2) receptor. CPD can also be caused by maternal vitamin K deficiency or warfarin teratogenicity.

Clinical Manifestations
These heterogeneous disorders are marked by ichthyosis and bone changes. Nearly all patients with the X-linked dominant form and approximately 25% of those with the recessive type have cutaneous lesions, ranging from severe, generalized erythema and scaling to mild hyperkeratosis. Rhizomelic chondrodysplasia punctata is associated with cataracts, hypertelorism, optic nerve atrophy, disproportionate shortening of the proximal extremities, psychomotor retardation, failure to thrive, and spasticity; most affected patients die in infancy. Patients with the X-linked dominant form have asymmetric, variable shortening of the limbs and a distinctive ichthyosiform eruption at birth. Thick, yellow, tightly adherent, keratinized plaques are distributed in a whorled pattern over the entire body. The eruption typically resolves in infancy and may be superseded by a follicular atrophoderma and patchy alopecia.

Additional features in all variants include cataracts and abnormal facies with saddle nose and frontal bossing. The pathognomonic defect, termed chondrodysplasia punctata, is stippled epiphyses in the cartilaginous skeleton. This defect, which is seen in various settings and inherited disorders, often in association with peroxisomal deficiency and disturbance of cholesterol biosynthesis, disappears by 3–4 yr of age.

OTHER SYNDROMES WITH ICHTHYOSIS
A number of other rare syndromes with ichthyosis as a consistent feature include the following: keratitis with ichthyosis and deafness (KID syndrome, connexin 26 gene), ichthyosis with defective hair having a banded pattern under polarized light and a low sulfur content (trichothiodystrophy), multiple sulfatase deficiency, neutral lipid storage disease with ichthyosis (Chanarin-Dorfman syndrome, CGI58 gene), and CHILD syndrome (Fig. 658-10; congenital hemidysplasia with ichthyosiform erythroderma and limb defects; NSDHL gene).

Palmoplantar Keratodermas
Excessive hyperkeratosis of the palms and soles may occur as a manifestation of a focal or generalized congenital hereditary skin disorder or may result from such chronic skin diseases as psoriasis, eczema, pityriasis rubra pilaris, lupus erythematosus, or postinfectious arthritis syndrome.

Diffuse Hyperkeratosis of Palms and Soles (Unna-Thost, and Vorner)
Unna-Thost and Vorner type palmoplantar keratodermas (PPKs), although clinically inseparable, were thought to be separate entities. They were separated histologically by the presence (Vorner) or absence (Unna-Thost) of epidermolytic hyperkeratosis. They represent the clinical spectrum of the same disease caused by mutations in keratin (KRT1 and KRT9 genes). This autosomal dominant disorder manifests in the 1st few mo of life as erythema that gradually progresses to sharply demarcated, hyperkeratotic, scaling plaques over the palms (Fig. 658-11) and soles. The margins of the plaques often remain red; plaques may extend along the lateral aspects of the hands and feet and onto the volar wrists and the heels. Hyperhidrosis is usually present, but hair, teeth, and nails are usually normal. Striate (DSG1, DSP, KRT1 genes) and punctate forms of palmar and plantar hyperkeratosis represent distinct entities.

Mal De Meleda (SLURP-1 Gene)
A rare, progressive autosomal recessive condition, mal de Meleda is characterized by erythema and thick scales on the palms, fingers, soles, and flexor aspects of the wrists, knees, and elbows. Hyperhidrosis, nail thickening or koilonychia, and eczema may also occur.

Vohwinkel Palmoplantar Keratoderma (Mutilating Keratoderma)
Vohwinkel PPK is a progressive autosomal dominant disease consisting of honeycombed hyperkeratosis of palms and soles, sparing the arches; starfish-like and linear keratoses on the dorsum of the hands, fingers, feet, and knees; and ainhum-like constriction of the digits that sometimes leads to autoamputation. Varying degrees of alopecia may be seen. Two forms have been identified. Vohwinkel PPK with ichthyosis is caused by mutations in the loricrin gene, and Vohwinkel PPK with deafness by mutations in connexin 26.

Papillon-Lefèvre Syndrome (Cathepsin C Gene)
An autosomal recessive erythematous hyperkeratosis of the palms and soles, Papillon-Lefèvre syndrome sometimes extends to the dorsal
hands and feet, elbows, and knees later in childhood. The PPK may be either diffuse, striate, or punctuate. This syndrome is characterized by periodontal inflammation, leading to loss of teeth by age 4-5 yr if untreated.

**Other Syndromes**

Keratoderma of palms and soles also occurs as a feature of some forms of ichthyosis and ectodermal dysplasia. Richner-Hanhart syndrome is an autosomal recessive focal palmoplantar keratoderma with corneal ulcers, progressive mental impairment, and a deficiency of tyrosine aminotransferase, which leads to tyrosinemia. Pachyonychia congenita is transmitted as an autosomal dominant trait with variable expressivity. The classic type I form (Jadassohn-Lewandowski syndrome) is due to mutations in the gene for keratin 16. Major features of the syndrome are onychogryposis; palmoplantar keratoderma; follicular hyperkeratosis, especially of the elbows and knees; and oral leukokeratosis. The nail dystrophy is the most striking feature and may be present at birth or develop early in life. The nails are thickened and tubular, projecting upward at the free edge to form a conical roof over a mass of subungual keratotic debris. Repeated paronychial inflammation may result in shedding of the nails. The feature seen most consistently among patients with this condition is keratoderma of the palms and soles. Additional associated features include hyperhidrosis of the palms and soles, and bullae and erosions on the palms and soles. Some patients have shown a selective cell-mediated defect in recognition and processing of *Candida*. Surgical removal of the nails and excision of the nail matrix have been helpful in some patients.

**Treatment**

Treatment for PPK is the same no matter what its cause. In mild cases, emollient therapy may suffice. Keratolytic agents such as salicylic acid, lactic acid, and urea creams may be required. Oral retinoids are the treatment of choice for severe cases unresponsive to topical therapy.

*Bibliography is available at Expert Consult.*
Bibliography


KELOID

Etiology and Pathogenesis
Keloids are usually induced by trauma and commonly follow ear piercing, burns, scalds, and surgical procedures. The resulting keloid is larger than the initial area of trauma to the skin. Certain individuals are predisposed to keloid formation; a familial tendency (recessive or dominant inheritance) or the presence of foreign material in the wound may have a pathogenic role. Keloids are a rare feature of Ehlers-Danlos syndrome, Rubinstein-Taybi syndrome, and pachydermoperiostosis. Keloids result from an abnormal fibrous wound healing response in which tissue repair and regeneration—regulation control mechanisms are lost. Collagen production is 20 times that seen in normal scars and the type I:type III collagen ratio is abnormally high. In keloids, tissue values of tumor growth factor-β and platelet-derived growth factor are elevated; fibroblasts are more sensitive to their effects, and their degradation rate is decreased.

Clinical Manifestations
A keloid is a sharply demarcated, benign, dense growth of connective tissue that forms in the dermis after trauma. The lesions are firm, raised, pink to hyperpigmented, and rubbery; they may be tender or pruritic. Sites of predilection are the face, earlobes (Fig. 659-1), neck, shoulders, upper trunk, sternum, and lower legs. In both keloids and hypertrophic scars, new collagen forms over a much longer period than in wounds that heal normally.

Histology
A keloid consists of whorled and interlaced hyalinized collagen fibers.

Differential Diagnosis
Keloids should be differentiated from hypertrophic scars, which remain confined to the site of injury and gradually involute over time.

Treatment
Young keloids may diminish in size if injected intraleionally at 4 wk intervals with triamcinolone suspension (10-40 mg/mL). At times, a more concentrated suspension is required. Large or old keloids may require surgical excision followed by intraleional injections of corticosteroid. The risk of recurrence at the same site argues against surgical excision alone, although earlobe keloids respond well to surgical excision, pressure dressings, and intraleional steroids. Placement of topical silicone gel sheeting over the keloid for several hours per day for several weeks may help in some patients.

STRIAE CUTIS DISTENSAE (STRETCH MARKS)

Etiology and Pathogenesis
Striae formation is common in adolescence. The most frequent causes are rapid growth, pregnancy, obesity, Cushing disease, and prolonged corticosteroid therapy. The pathogenesis is unknown, but the occurrence of alterations in elastic fibers is thought to be the primary process.

Clinical Manifestations
These thinned, depressed, erythematous bands of atrophic skin eventually become silvery, opalescent, and smooth. They occur most frequently in areas that have been subject to distention, such as the lower back (Fig. 659-2), buttocks, thighs, breasts, abdomen, and shoulders.

Differential Diagnosis
Striae distensae resemble atrophic scars.

Treatment
Controlled trials of treatments for striae are lacking; however, striae tend to spontaneously become less conspicuous as the color fades with time.
Corticosteroid-Induced Atrophy

**Etiology and Pathogenesis**
Both topical and systemic corticosteroid treatment can result in cutaneous atrophy. This is particularly common when a potent or superpotent topical corticosteroid is applied under occlusion or to an intertriginous area for a prolonged period. Keratinocyte growth is decreased, but epidermal maturation is accelerated, resulting in a thinning of the epidermis and stratum corneum. Fibroblast growth and function are also decreased, leading to the dermal changes. The mechanism involves inhibition of synthesis of collagen type I, noncollagenous proteins, and total protein content of the skin, along with progressive reduction of dermal proteoglycans and glycosaminoglycans.

**Clinical Manifestations**
Affected skin is thin, fragile, smooth, and semitransparent, with telangiectasias, prominent veins, and loss of normal skin markings.

**Histology**
Histopathologically, one sees thinning of the epidermis. Spaces between dermal collagen and elastic fibers are small, producing a more compact but thin dermis.

**Treatment**
Optimal treatment is prevention by proper use of topical steroids to avoid side effects.

Granuloma Annulare

**Etiology and Pathogenesis**
The cause of granuloma annulare is unknown. Some cases of granuloma annulare, particularly the generalized form, may be associated with diabetes mellitus or with anterior uveitis. However, most cases are seen in healthy children.

**Clinical Manifestations**
This common dermatosis occurs predominantly in children and young adults. Affected children are usually healthy. Typical lesions begin as firm, smooth, erythematous papules. They gradually enlarge to form annular plaques with a papular border and a normal, slightly atrophic or discolored central area up to several centimeters in size. Lesions may occur anywhere on the body, but mucous membranes are spared. Favored sites include the dorsum of the hands (Fig. 659-3) and feet. The disseminated papular form is rare in children. Subcutaneous granuloma annulare tends to develop on the scalp and limbs, particularly in the pretibial area. These lesions are firm, usually nontender, skin-colored nodules. Perforating granuloma annulare is characterized by the development of a yellowish center in some of the superficial papular lesions as a result of transepidermal elimination of altered collagen.

Differential Diagnosis
Annular lesions are often mistaken for tinea corporis because of the elevated advancing border. They differ in that they are not scaly. Papular lesions, another variant, may simulate rheumatoid nodules, particularly when grouped on the fingers and elbows.

**Histology**
The lesion of granuloma annulare consists of a granuloma with a central area of necrotic collagen; mucin deposition; and a peripheral palisading infiltrate of lymphocytes, histiocytes, and foreign body giant cells. The pattern resembles that of necrobiosis lipoidica and rheumatoid nodule, but subtle histologic differences usually permit differentiation.

**Treatment**
The eruption persists for months to years, but spontaneous resolution without residual change is usual; 50% of lesions clear within 2 yr. Application of a potent or superpotent topical corticosteroid preparation or intralesional injections (5-10 mg/mL) of corticosteroid may hasten involution, but nonintervention is usual.

Necrobiosis Lipoidica

**Etiology and Pathogenesis**
The cause of necrobiosis lipoidica is unknown, but 50-75% of patients have diabetes mellitus; necrobiosis lipoidica occurs in 0.3% of all diabetic patients.

**Clinical Manifestations**
This disorder manifests as erythematous papules that evolve into irregularly shaped, sharply demarcated, yellow, sclerotic plaques with central telangiectasia and a violaceous border. Scaling, crusting, and ulceration are frequent. Lesions develop most commonly on the shins (Fig. 659-4). Slow extension of a given lesion over the years is usual, but long periods of quiescence or complete healing with scarring may occur.

**Histology**
Poorly defined areas of necrobiotic collagen are seen throughout, but primarily low in the dermis, associated with mucin deposition. Surrounding the necrobiotic, disordered areas of collagen is a palisading lymphohistiocytic granulomatosus infiltrate. Some lesions are more characteristically granulomatous, with limited necrobiosis of collagen.

**Differential Diagnosis**
Necrobiosis lipoidica must be differentiated clinically from xanthomas, morphea, granuloma annulare, erythema nodosum, and pretibial myxedema.
Treatment
The lesions persist despite good control of the diabetes but may improve minimally after applications of high-potency topical steroids or local injection of a corticosteroid. Pentoxifylline has also been used.

LICHEN SCLEROSUS
Etiology and Pathogenesis
The cause of lichen sclerosis is unknown. Several studies have identified the presence of autoantibodies to the glycoprotein extracellular matrix protein 1 (ECM-1). The exact role of these antibodies are currently under investigation, however.

Clinical Manifestations
Lichen sclerosus manifests initially as shiny, indurated, ivory-colored papules, often with a violaceous halo. The surface shows prominent dilated pilosebaceous or sweat duct orifices that often contain yellow or brown plugs. The papules coalesce to form irregular plaques of variable size, which may develop hemorrhagic bullae in their margins. In the later stages, atrophy results in a depressed plaque with a wrinkled surface. This disorder occurs more commonly in girls than in boys. Sites of predilection in girls are the vulvar (Fig. 659-5), perianal, and perineal skin. Extensive involvement may produce a sclerotic, atrophic plaque of hourglass configuration; shrinkage of the labia and stenosis of the introitus may result. Vaginal discharge precedes vulvar lesions in approximately 20% of patients. In boys, the prepuce and glans penis are often involved, usually in association with phimosis; most boys with the disorder were not circumcised early in life. Sites elsewhere on the body that are most commonly involved include the upper trunk, the neck, the axillae, the flexor surfaces of wrists, and the areas around the umbilicus and the eyes. Pruritus may be severe.

Differential Diagnosis
In children, lichen sclerosus is most frequently confused with focal morphea (see Chapter 160), with which it may coexist. In the genital area, it may be mistakenly attributed to sexual abuse.

Histology
Biopsy is diagnostic, revealing hyperkeratosis with follicular plugging, hydropic degeneration of basal cells, a bandlike dermal lymphocytic infiltrate, homogenized collagen, and thinned elastic fibers in the upper dermis.

Treatment
Vulvar lichen sclerosus in childhood usually improves with puberty but does not always resolve completely, and symptoms can recur throughout life. Long-term observation for the development of squamous cell carcinoma is necessary. Superpotent topical corticosteroids provide relief from pruritus and produce clearing of lesions, including those in the genital area. Topical tacrolimus and pimecrolimus have also been used. It is not known how response to treatment affects long-term cancer risk.

MORPHEA
Etiology and Pathogenesis
Morphea is a sclerosing condition of the dermis and subcutaneous tissue of unknown etiology.

Clinical Manifestations
Morphea is characterized by solitary, multiple, or linear circumscribed areas of erythema that evolve into indurated, sclerotic, atrophic plaques (Fig. 659-6), later healing, or “burning out” with pigment change. It is seen more commonly in females. The most common types of morphea are plaque and linear. Morphea can affect any area of skin. When confined to the frontal scalp, forehead, and midface in a linear band, it is referred to as en coup de sabre. When located on one side of the face, it is called progressive hemifacial atrophy. These forms of morphea carry a poorer prognosis because of the associated underlying central nervous system involvement or musculoskeletal atrophy that can be cosmetically disfiguring. Linear morphea over a joint may lead to restriction of mobility (Fig. 659-7). Pansclerotic morphea is a rare, severe, disabling variant.

Differential Diagnosis
The differential diagnosis of morphea includes granuloma annulare, necrobiosis lipoidica, lichen sclerosis, and late-stage Lyme disease (acrodermatitis chronica atrophicans).
SCLEREDEMA (SCLEREDEMA ADULTORUM, SCLEREDEMA OF BUSCHE)

Etiology and Pathogenesis

The cause of scleredema is unknown. There are 3 types. Type 1 (55% of cases) is preceded by a febrile illness, often related to an upper or lower respiratory infection (streptococcal most commonly). Type 2 (25%) is associated with paraproteinemias, including multiple myeloma. Type 3 (20%) is seen in diabetes mellitus.

Clinical Manifestations

Fifty percent of patients with scleredema are younger than 20 yr old and almost always have type 1. Onset of type 1 is sudden, with brawny edema of the face and neck that spreads rapidly to involve the thorax and arms in a sweater distribution; the abdomen and legs are usually spared. The face acquires a waxy, mask-like appearance. The involved areas feel indurated and woody, are nonpitting, and are not sharply demarcated from normal skin. The overlying skin is normal in color and is not atrophic.

Onset in patients with type 2 and type 3 scleredema may occur insidiously. Systemic involvement, which is uncommon and usually associated with types 2 and 3, is marked by thickening of the tongue; dysarthria; dysphagia; restriction of eye and joint movements; and pleural, pericardial, and peritoneal effusions. Electrocardiographic changes may also be observed. Laboratory data are not helpful.

Differential Diagnosis

Scleredema must be differentiated from scleroderma (see Chapter 160), morphea, myxedema, trichinosis, dermatomyositis, sclerema neonatorum, and subcutaneous fat necrosis.

Histology

Skin biopsy demonstrates an increase in dermal thickness as a result of swelling and homogenization of the collagen bundles, which are separated by large interfibrous spaces. Special stains can identify increased amounts of mucopolysaccharides in the dermis of patients with scleredema.

Treatment

In type 1 scleredema, the active phase of the disease persists for 2–8 wk; spontaneous and complete resolution usually occurs in 6 mo to 2 yr. Recurrent attacks are unusual. In type 2 and 3, disease is slowly progressive. There is no specific therapy.

LIPOID PROTEINOSIS (URBACH-WIETHE DISEASE, HYALINOSIS CUTIS ET MUCOSAE)

Etiology and Pathogenesis

Lipoid proteinosis, an autosomal recessive disorder, is caused by mutations in the ECM-1 gene, which encodes the ECM-1 protein. ECM-1 has a functional role in the structural organization of the dermis by binding to perlecan, matrix metalloproteinase 9, and fibulin. Pathogenesis involves infiltration of hyaline material into the skin, oral cavity, larynx, and internal organs.

Clinical Manifestations

Lipoid proteinosis may be noted initially in early infancy as hoarseness. Skin lesions appear during childhood and consist of yellowish papules and nodules that may coalesce to form plaques. The classic sign is beaded papules on the eyelids. Lesions also occur on the face, forearms, neck, genitals, dorsum of the fingers, and scalp, where they result in patchy alopecia. Similar deposits are found on the lips, undersurface of the tongue, fauces, uvula, epiglottis, and vocal cords. The tongue becomes enlarged and feels firm on palpation. The patient may be unable to protrude the tongue. Pock-like atrophic scars may develop on the face. Hypertrophic, hyperkeratotic nodules occur at sites of friction, such as the elbows and knees; the palms may be diffusely thickened. The disease progresses until early adult life, but the prognosis is good. Symmetric ossification lateral to the sella turcica in the medial temporal region, identifiable roentgenographically, is pathognomonic but is not always present. Involvement of the larynx can lead to respiratory compromise, particularly in infancy, necessitating tracheostomy. Associated anomalies include dental abnormalities, epilepsy, and recurrent parotitis as a result of infiltrates in the Stensen duct. Virtually any organ can be involved.

Histology

The distinctive histologic pattern in lipoid proteinosis includes dilation of dermal blood vessels and infiltration of homogeneous eosinophilic extracellular hyaline material along capillary walls and around sweat ducts. Virtually any organ can be involved.

MACULAR ATROPHY (ANETODERMA)

Etiology and Pathogenesis

Anetoderma is characterized by circumscribed areas of slack skin associated with loss of dermal substance. This disorder may have no associated underlying disease (primary macular atrophy) or may develop after an inflammatory skin condition. Secondary macular atrophy may be a result of direct destruction of dermal elastin or elastolysis on an immunologic basis, especially the presence of antiphospholipid antibodies, which are related to autoimmune disorders. The elastolysis may then be a result of release of elastase from inflammatory cells.

Clinical Manifestations

Lesions vary from 0.5–1.0 cm in diameter and, if inflammatory, may initially be erythematous. They subsequently become thin, wrinkled,
and blue-white or hypopigmented. The lesions often protrude as small outpouchings that, on palpation, may be readily indented into the subcutaneous tissue because of the dermal atrophy. Sites of predilection include the trunk, thighs, upper arms, and, less commonly, the neck and face. Lesions remain unchanged for life; new lesions often continue to develop for years.

**Histology**

All types of macular atrophy show focal loss of elastic tissue on histopathologic examination, a change that may not be recognized unless special stains are used.

**Differential Diagnosis**

Lesions of anetoderma occasionally resemble morphea, lichen sclerosus, focal dermal hypoplasia, atrophic scars, or end-stage lesions of chronic bullous dermatoses.

**Treatment**

There is no effective therapy for macular atrophy.

**CUTIS LAXA (DERMATOMEGALY, GENERALIZED ELASTOLYSIS)**

**Etiology and Pathogenesis**

Cutis laxa is a heterogeneous group of disorders related to abnormalities in elastic tissue. It may be autosomal recessive (type I: fibulin 5 and fibulin 4 genes; type II: ATP6V0A2 gene), autosomal dominant (elastin and fibulin 5 genes), X-linked (Cu²⁺-transporting adenosine triphosphatase, α-polypeptide), or acquired. Acquired cutis laxa has developed after a febrile illness, inflammatory skin diseases such as lupus erythematosus or erythema multiforme, amyloidosis, urticaria, angioedema, and hypersensitivity reactions to penicillin, and in infants born to women who were taking penicillamine.

**Clinical Manifestations**

There may be widespread folds of lax skin, or changes may be mild and limited in extent, resembling anetoderma. Patients with severe cutis laxa have characteristic facial features, including an aged appearance (Fig. 659-8), a hooked nose with everted nostrils, a short columella, a long upper lip, and everted lower eyelids. The skin is also lax on the body and may resemble an ill-fitting suit. Hyperelasticity and hypermobility of the joints are not present as they are in the Ehlers-Danlos syndrome. Many infants have a hoarse cry, probably as a result of laxity of the vocal cords. Tensile strength of the skin is normal.

The dominant form of cutis laxa may develop at any age and is generally benign. When it manifests in infancy, it may be associated with intrauterine growth restriction, ligamentous laxity, and delayed closure of the fontanelles. Pulmonary emphysema and mild cardiovascular manifestations may also occur. Patients with the more common recessive form of the disease are susceptible to severe complications, such as multiple hernias, rectal prolapse, diaphragmatic atony, diverticula of the gastrointestinal and genitourinary tracts, cor pulmonale, emphysema, pneumothoraces, peripheral pulmonary artery stenosis, and aortic dilation. Characteristic facial features include downward-slanting palpebral fissures, a broad, flat nose, and large ears. Skeletal anomalies, dental caries, growth retardation, and developmental delay also occur. Such patients often have a shortened life span.

Cutis laxa-like skin changes may also be seen in association with multiple other syndromes, including De Bary syndrome, Lenz-Majewski syndrome, hyperostotic dwarfism, SCARF (skeletal abnormalities, cutis laxa craniofacial syndrome, ambiguous genitalia, retardation, facial abnormalities) syndrome, wrinkling skin syndrome, and Costello syndrome.

**Histology**

Histologically, elastic tissue is reduced throughout the dermis, with fragmentation, distention, and clumping of the elastic fibers.

**Treatment**

Treatment for cutis laxa is supportive.

**EHLERS-DANLOS SYNDROME**

Ehlers-Danlos syndrome (EDS) is a group of genetically heterogeneous connective tissue disorders. Affected children appear normal at birth, but skin hyperelasticity, fragility of the skin and blood vessels, delayed wound healing, and joint hypermobility (Fig. 659-9) develop. The essential defect is a quantitative deficiency of fibrillar collagen. Additional features include autonomic dysfunction (hypermobility types) characterized by recurrent or chronic musculoskeletal pain, orthostatic intolerance, sudomotor dysfunction, and gastrointestinal disturbances (gastroparesis, diarrhea, constipation). Dysautonomic features may be exacerbated by vasoactive medications. In addition, patients with EDS have an increased incidence of Chiari type 1 malformations, perhaps due to hypermobility of the occipitoatlantal and atlantoaxial joints or poor connective tissue support. Basilar impression symptoms from herniation may contribute to the morbidity of EDS. In patients with a Chiari type 1 malformation there may also be a spinal cord syrinx distal to the malformation. Pulmonary complications may include pneumothorax, hemoptysis, bullous lung disease, and tracheomegaly.

**Classification**

EDS has been reclassified into 6 clinical recognized forms and 1 unclassified group (Table 659-1).
### Table 659-1: Ehlers-Danlos Syndrome

<table>
<thead>
<tr>
<th>TYPE</th>
<th>FORMER NAME</th>
<th>CLINICAL FEATURES*</th>
<th>INHERITANCE</th>
<th>OMIM†</th>
<th>MOLECULAR DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>EDS I and II</td>
<td>Joint hypermobility; skin hyperextensibility; atrophic scars; smooth, velvety skin; subcutaneous spheroids</td>
<td>AD</td>
<td>130000</td>
<td>Structure of type V collagen because of mutations in COL5A1, COL5A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>130010</td>
<td></td>
</tr>
<tr>
<td>Hypermobility</td>
<td>EDS III</td>
<td>Joint hypermobility; some skin hyperextensibility, with or without smooth, velvety texture</td>
<td>AD</td>
<td>130020</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AR</td>
<td>225320</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tenascin-X (TNX)</td>
</tr>
<tr>
<td>Vascular</td>
<td>EDS IV</td>
<td>Thin skin; easy bruising; pinched nose; acrogeria; rupture of large-caliber and medium-caliber arteries, uterus, and large bowel</td>
<td>AD</td>
<td>130050</td>
<td>Deficient type III collagen (COL3A1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(225350)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(225360)</td>
<td></td>
</tr>
<tr>
<td>Kyphoscoliotic</td>
<td>EDS VI</td>
<td>Joint hypermobility; congenital, progressive rupture; scleros; scleral fragility with globe rupture; tissue fragility, aortic dilation, MVP</td>
<td>AR</td>
<td>225400</td>
<td>Deficiency of lysyl hydroxylase</td>
</tr>
<tr>
<td>Arthrochalasis</td>
<td>EDS VII A</td>
<td>Joint hypermobility, severe, with subluxations, congenital hip dislocation; skin hyperextensibility, tissue fragility</td>
<td>AD</td>
<td>130060</td>
<td></td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>EDS VII C</td>
<td>Severe skin fragility; decreased skin elasticity, easy bruising; hernias; premature rupture of fetal membranes</td>
<td>AR</td>
<td>225410</td>
<td>No cleavage of amino terminus of type I procollagen because of mutations in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>Unclassified types</td>
<td>EDS V</td>
<td>Classic features</td>
<td>XL</td>
<td>305200</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>EDS VIII</td>
<td>Classic features and periodontal disease</td>
<td>AD</td>
<td>130080</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>EDS X</td>
<td>Mild classic features, MVP</td>
<td>?</td>
<td>225310</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>EDS XI</td>
<td>Joint instability</td>
<td>AD</td>
<td>147900</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>EDS IX</td>
<td>Classic features; occipital horns</td>
<td>XL</td>
<td>309400</td>
<td>Allelic to Menkes syndrome</td>
</tr>
<tr>
<td></td>
<td>EDS, progeroid form</td>
<td>Classic features and premature aging</td>
<td>AR</td>
<td>130700</td>
<td>Deficiency of galactosyltransferase I</td>
</tr>
</tbody>
</table>

*Listed in order of diagnostic importance.
†Entries in Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). Available at: [http://omim.org/](http://omim.org/)
AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers-Danlos syndrome; MVP, mitral valve prolapse; XL, X-linked.


**Classic (COL5A1, COL5A2, COL1A1 Genes; Previously EDS Type I—Gravis, EDS Type II—MITIS)**

This autosomal dominant disorder is characterized by premature birth caused by rupture of membranes, skin hyperelasticity and fragility, easy bruising, generalized and severe joint hypermobility, scoliosis, and mitral valve prolapse. Insignificant lacerations may form gaping wounds that leave broad, atrophic, papyraceous scars. Additional cutaneous manifestations include molluscoid pseudotumors over pressure points from accumulations of connective tissue and piezogenic papules (fat herniation into the dermis) (Fig. 659-10). Life expectancy is not reduced.

**Hypermobile (COL3A1 Gene; Previously EDS Type III)**

This disorder has autosomal dominant inheritance and manifests as generalized severe joint hypermobility and minimal skin manifestations. Musculoskeletal pain is common, and osteoarthritis may develop prematurely.

**Vascular (COL3A1 Gene; Previously EDS Type IV—Arterial Ecchymotic)**

This autosomal dominant disorder shows the most pronounced dermal thinning of all. Consequently, the underlying venous network is prominent. The skin has minimal hyperextensibility, and the joints are not hypermobile, except perhaps during childhood. Premature birth, extensive ecchymoses from trauma, a high incidence of keloids, rupture of the bowel (especially the colon), uterine rupture during pregnancy, and premature aging are characteristic. Life expectancy is not reduced.

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*Figure 659-10 Piezogenic papules on the medial aspects of the heels in a 41-year-old patient with Ehlers-Danlos syndrome (top) and his 2-year-old daughter (bottom). (From Poppe H, Hamm H: Piezogenic papules in Ehlers-Danlos syndrome. J Pediatr 163:1788, 2013.)*
rupture of the great vessels, dissecting aortic aneurysm, and stroke all contribute to the increased morbidity and shortened life span. Patients should be advised to avoid becoming pregnant, avoid activities that raise intracranial pressure as a result of a Valsalva maneuver, such as trumpet playing, and minimize trauma to the skin. Celioprolol, a β1 antagonist and a β2 agonist (vasodilatation), may reduce vascular events.

**Kyphoscoliosis (Lysyl Hydroxyylase [PLOD Gene] Deficiency; Previously EDS Type VI)**

Patients with this autosomal recessive type have joint hyperextensibility, hypotonia, kyphoscoliosis, fragile cornea, keratoconus, skin hyperelasticity, and fragile bones. Prenatal diagnosis is available through measurement of lysyl hydroxyylase activity in amniocytes. The diagnosis can also be confirmed by detection of decreased lysyl hydroxyylase activity in cultured dermal fibroblasts.

**Arthrochalasia (COLA1A Gene, Type A; COLA12 Gene, Type B; Previously EDS Types VIIA and B—Arthrochalasis Multiplex Congenita)**

The A type is an autosomal dominant disorder characterized by short stature, marked joint hyperextensibility and dislocation, and moderate hyperelasticity and bruising of skin. The B type is autosomal dominant and is characterized by skin hyperelasticity and marked joint hypermobility.

**Dermatosparaxis (Type 1 Collagen N-Peptidase; Previously EDS Type VIIC)**

This autosomal recessive condition that includes premature rupture of membranes; delayed closure of fontanelles; skin fragility and laxity; easy bruising; growth retardation; short limbs; umbilical hernia; and characteristic facies with micrognathia, jowls, and prominent, puffy eyelids.

**Differential Diagnosis**

EDS has been confused with cutis laxa, but the features of the 2 disorders differ considerably. The skin of patients with cutis laxa hangs in redundant folds, whereas the skin of those with EDS is hyperextensible and snaps back into place when stretched. Because of the marked skin fragility in EDS, minor trauma results in ecchymoses, bleeding, and poor healing with atrophic cigarette-paper scars, which are most prominent on the forehead and lower legs and over pressure points. Surgical procedures are fraught with risk; dehiscence of wounds is common.

Joint hypermobility is seen in other connective tissue disorders (Fig. 659-11). Joint hypermobility is scored with the 9 point Beighton score (Table 659-2) and can be assessed by history (Table 659-3).

Figure 659-12 provides an initial approach to the diagnosis of EDS.

---

**Table 659-2** The Nine-Point Beighton Hypermobility Score

<table>
<thead>
<tr>
<th>The ability to:</th>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Passively dorsiflex the fifth metacarpophalangeal joint to ≥90°</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2. Oppose the thumb to the volar aspect of the ipsilateral forearm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3. Hyperextend the elbow to ≥10°</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. Hyperextend the knee to ≥10°</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5. Place hands flat on the floor without bending the knees</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total 9</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One point may be gained for each side for maneuvers 1-4 so the hypermobility score will have a maximum of 9 points if all are positive.


**Table 659-3** A Five-Part Questionnaire for Identifying Hypermobility

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?  
2. Can you now (or could you ever) bend your thumb to touch your forearm?  
3. As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?  
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?  
5. Do you consider yourself double-jointed?

*Answer in the affirmative to 2 or more questions suggests hypermobility with sensitivity 80-85% and specificity 80-90%*


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Figure 659-11 A Venn diagram illustrating the overlap features between the 4 major heritable disorders of connective tissue. Joint hypermobility syndrome (JHS) maintains a central position sharing key features with Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome, and is seen as a benign form of all 3 heritable disorders of connective tissue “rolled into one.” (From Hakim A, Grahame R: Joint hypermobility. Best Pract Res Clin Rheumatol 17:989–1004, 2003, Fig. 1.)

Figure 659-12 Diagnostic flow chart for Ehlers-Danlos syndrome, classic type. (From De Paepre A, Malfait F: The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genet 82:1–11, 2012, Fig. 3.)
PSEUDOXANTHOMA ELASTICUM
Etiology and Pathogenesis

Pseudoxanthoma elasticum (PXE) is a primary disorder of elastic tissue. The overwhelming majority of cases are caused by mutations in the \textit{ABCC6} gene. The primary abnormality seen in PXE is an accumulation of mineralized tissue in the skin, Bruch membrane in the retina, and vessel walls. Although other forms of PXE have been postulated, their existence is now debated.

Clinical Manifestations

Onset of skin manifestations often occurs during childhood, but the changes produced by early lesions are subtle and may not be recognized. The characteristic \textit{pebbly, “plucked chicken skin” cutaneous lesions} are 1-2 mm, asymptomatic, yellow papules that are arranged in a linear or reticulated pattern or in confluent plaques. Preferred sites are the flexural neck (Fig. 659-13), axillary and inguinal folds, umbilicus, thighs, and antecubital and popliteal fossae. As the lesions become more pronounced, the skin acquires a velvety texture and droops in lax, inelastic folds. The face is usually spared. Mucous membrane lesions may involve the lips, buccal cavity, rectum, and vagina. There is involvement of the connective tissue of the media, and intima of blood vessels, Bruch membrane of the eye, and endocardium or pericardium may result in visual disturbances, angioid streaks in Bruch membrane, intermittent claudication, cerebral and coronary occlusion, hypertension, and hemorrhage from the gastrointestinal tract, uterus, or mucosal surfaces. Women with PXE have an increased risk of miscarriage in the 1st trimester. Arterial involvement generally manifests in adulthood, but claudication and angina have occurred in early childhood.

Pathology

Histopathologic examination shows fragmented, swollen, and clumped elastic fibers in the middle and lower third of the dermis. The fibers stain positively for calcium. Collagen in the vicinity of the altered elastic fibers is reduced in amount and is split into small fibers. Aberrant calcification of the elastic fibers of the internal elastic lamina of arteries in PXE leads to narrowing of vessel lumina.

Treatment

There is no effective treatment for PXE, although laser therapy may help prevent retinal hemorrhage. The use of oral phosphate binders has shown promise in decreasing calcification of elastic fibers.

ELASTOSIS PERFORANS SERPIGINOSA
Etiology and Pathogenesis

Elastosis perforans serpiginosa (EPS) is characterized by the extrusion of altered elastic fibers through the epidermis. The primary abnormality is probably in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue.

Clinical Manifestations

This is an unusual skin disorder in which 1-3 mm, firm, skin-colored, keratotic papules tend to cluster in arcuate and annular patterns on the posterolateral neck and limbs (Fig. 659-14) and occasionally on the face and trunk. Onset usually occurs in childhood or adolescence. A papule consists of a circumscribed area of epidermal hyperplasia that communicates with the underlying dermis by a narrow channel. There is a great increase in the amount and size of elastic fibers in the upper dermis, particularly in the dermal papillae. Approximately 30% occur in association with osteogenesis imperfecta, Marfan syndrome, PXE, EDS, Rothmund-Thomson syndrome, scleroderma, acrogeria, and Down syndrome. EPS has also occurred in association with penicillamine therapy.

Histology

Histopathology reveals a hyperplastic epidermis with extrusion of abnormal elastic fibers and a lymphocytic superficial infiltrate.

Differential Diagnosis

Differential diagnosis of EPS includes tinea corporis, perforating granuloma annulare, reactive perforating collagenosis, lichen planus, creeping eruption, and porokeratosis of Mibelli.

Treatment

Treatment of EPS is ineffective; however, the lesions are asymptomatic and may disappear spontaneously.

REACTIVE PERFORATING COLLAGENOSIS
Etiology and Pathogenesis

The primary process in reactive perforating collagenosis represents transepidermal elimination of altered collagen. A familial autosomal recessive form has been described.

Clinical Manifestations

Reactive perforating collagenosis usually manifests in early childhood as small papules on the dorsal areas of the hands and forearms, elbows, knees, and, sometimes, face and trunk. Over a period of several weeks, the papules enlarge to 5-10 mm, become umbilicated, and develop keratotic plugs in their centers (Fig. 659-15). Individual lesions resolve spontaneously in 2-4 mo, leaving hypopigmented macules or scars. Lesions may recur in crops; may undergo a linear Koebner phenomenon; and may form in response to cold temperatures or superficial trauma such as abrasions, insect bites, and acne lesions.
manifestations of the disease are at least partly a result of the release of histamine and heparin from mast cell granules; although heparin is present in significant amounts in mast cells, coagulation disturbances occur only rarely. The vasodilator prostaglandin D2 or its metabolite appears to exacerbate the flushing response. Serum tryptase values can be elevated.

**Clinical Manifestations**

**Solitary mastocytomas** are usually 1-5 cm in diameter. Lesions may be present at birth or may arise in early infancy at any site. The lesions may manifest as recurrent, evanescent wheals or bullae; in time, an infiltrated, pink, yellow, or tan, rubbery plaque develops at the site of whealing or blistering (Fig. 659-16). The surface acquires a pebbly, orange peel–like texture, and hyperpigmentation may become prominent. Stroking or trauma to the nodule may lead to urtication (Darier sign) as a result of local histamine release; rarely, systemic signs of histamine release become apparent.

**Histology**

Collagen in the papillary dermis is engulfed within a cup-shaped perforation in the epidermis. The central crater contains pyknotic inflammatory cells and keratinous debris.

**Differential Diagnosis**

EPS and Kyrle disease may mimic reactive perforating collagenosis.

**Treatment**

Reactive perforating collagenosis resolves spontaneously in 6-8 wk. Topical retinoic acid enhances the resolution.

**XANTHOMAS**

See Chapter 86.

**FABRY DISEASE**

See Chapter 86.

**MUCOPOLYSACCHARIDOSES**

See Chapter 88.

In several of the mucopolysaccharidoses, thick, rough, inelastic skin, particularly on the extremities, and generalized hirsutism are characteristic but nonspecific features. Telangiectasias on the face, forearms, trunk, and legs have been observed in Scheie and Morquio syndromes. In some patients with Hunter syndrome, ivory-colored, distinctive firm papulonodules with a corrugated surface texture are grouped into symmetric plaques on the upper trunk (Fig. 659-16), arms, and thighs. Onset of these unusual lesions occurs in the 1st decade of life, and spontaneous disappearance has been noted.

**MASTOCYTOSIS**

**Etiology and Pathogenesis**

Mastocytosis encompasses a spectrum of disorders that range from solitary cutaneous nodules to diffuse infiltration of skin associated with involvement of other organs (Table 659-4). All of the disorders are characterized by aggregates of mast cells in the dermis. There are 4 types of mastocytoses: solitary mastocytoma, urticaria pigmentosa (2 forms), diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans. The 2 forms of urticaria pigmentosa are the childhood variant, which resolves without sequelae, and the form that may start in either childhood or adult life and is associated with a mutation (most commonly the D816V mutation) in the stem cell factor gene. Stem cell factor (mast cell growth factor), which can be secreted by keratinocytes, stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. The local and systemic manifestations of the disease are at least partly a result of the release of histamine and heparin from mast cell granules; although heparin is present in significant amounts in mast cells, coagulation disturbances occur only rarely. The vasodilator prostaglandin D2 or its metabolite appears to exacerbate the flushing response. Serum tryptase values can be elevated.

**Clinical Manifestations**

**Solitary mastocytomas** are usually 1-5 cm in diameter. Lesions may be present at birth or may arise in early infancy at any site. The lesions may manifest as recurrent, evanescent wheals or bullae; in time, an infiltrated, pink, yellow, or tan, rubbery plaque develops at the site of whealing or blistering (Fig. 659-17). The surface acquires a pebbly, orange peel–like texture, and hyperpigmentation may become prominent. Stroking or trauma to the nodule may lead to urtication (Darier sign) as a result of local histamine release; rarely, systemic signs of histamine release become apparent.

**Histology**

Collagen in the papillary dermis is engulfed within a cup-shaped perforation in the epidermis. The central crater contains pyknotic inflammatory cells and keratinous debris.

**Differential Diagnosis**

EPS and Kyrle disease may mimic reactive perforating collagenosis.

**Treatment**

Reactive perforating collagenosis resolves spontaneously in 6-8 wk. Topical retinoic acid enhances the resolution.

**Table 659-4 Mastocytosis Classification**

<table>
<thead>
<tr>
<th>Cutaneous mastocytosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Urticaria pigmentosa:</td>
</tr>
<tr>
<td>(a) Classic infantile type; (b) Chronically with stem cell factor mutations</td>
</tr>
<tr>
<td>2. Diffuse cutaneous mastocytosis</td>
</tr>
<tr>
<td>3. Mastocytoma of the skin</td>
</tr>
<tr>
<td>4. Telangiectasia macularis eruptiva perstans</td>
</tr>
</tbody>
</table>

Systemic mastocytosis (without an associated hematologic non–mast cell disorder or leukemic mast cell disease):

1. Systemic indolent mastocytosis
2. Systemic smoldering mastocytosis
3. Systemic mastocytosis with an associated hematologic non–mast cell disorder:
   1. Myeloproliferative syndrome
   2. Myelodysplastic syndrome
   3. Acute myeloid leukemia
   4. Non-Hodgkin lymphoma

Systemic aggressive mastocytosis

Mast cell leukemia

Mast cell sarcoma

Extracutaneous mastocytoma

The second type of urticaria pigmentosa may begin in infancy but typically develops in adulthood. This type does not resolve, and new lesions continue to develop throughout life. It is associated with mutations in the stem cell factor gene. Patients with this type of mastocytosis are the population in whom systemic involvement may develop.

Systemic mastocytosis is marked by an abnormal increase in the number of mast cells in other than cutaneous tissues. It occurs in approximately 5-10% of patients with mutant stem cell factor–related mastocytosis and is uncommon in children. Bone lesions may be silent but are detectable radiologically as osteoporotic or osteosclerotic areas, principally in the axial skeleton. Gastrointestinal tract involvement may produce complaints of abdominal pain, nausea, vomiting, diarrhea, steatorrhea, and bloating. Mucosal infiltrates may be detectable by barium studies or by small bowel biopsy. Peptic ulcers also occur. Hepatosplenomegaly as a result of mast cell infiltrates and fibrosis has been described, as has mast cell proliferation in lymph nodes, kidneys, periadrenal fat, and bone marrow. Abnormalities in the peripheral blood, such as anemia, leukocytosis, and eosinophilia, are noted in approximately 30% of patients. Mast cell leukemia may occur.

Diffuse cutaneous mastocytoma is characterized by diffuse involvement of the skin rather than discrete hyperpigmented lesions. Affected patients are usually normal at birth and demonstrate features of the disorder after the 1st few mo of life. Rarely, the condition may present with intense generalized pruritus in the absence of visible skin changes. The skin usually appears thickened and pink to yellow and may have a doughy feel and a texture resembling an orange peel. Surface changes are accentuated in flexural areas. Recurrent bullae (Fig. 659-19), intractable pruritus, and flushing attacks are common, as is systemic involvement.

Telangiectasia macularis eruptiva perstans is another variant that consists of telangiectatic hyperpigmented macules that are usually localized to the trunk. These lesions do not urticate when stroked. This form of the disease is seen primarily in adolescents and adults.

**Urticaria pigmentosa** is the most common form of mastocytosis. In the first type of urticaria pigmentosa, the classic infantile type, lesions may be present at birth but more often erupt in crops in the 1st several mo to 2 yr of age. New lesions seldom arise after age 3-4 yr. In some cases, early bullous or urticarial lesions fade, only to recur at the same site, ultimately becoming fixed and hyperpigmented. In others, the initial lesions are hyperpigmented. Vesiculation usually abates by 2 yr of age. Individual lesions range in size from a few millimeters to several centimeters and may be macular, papular, or nodular. They range in color from yellow-tan to chocolate brown and often have ill-defined borders (Fig. 659-18). Larger nodular lesions, like solitary mastocytomas, may have a characteristic orange peel texture. Lesions of urticaria pigmentosa may be sparse or numerous and are often symmetrically distributed. Palms, soles, and face are sometimes spared, as are the mucous membranes. The rapid appearance of erythema and whealing in response to vigorous stroking of a lesion can usually be elicited; dermographism of intervening normal skin is also common. Affected children can have intense pruritus. Systemic signs of histamine release, such as hypotension, syncope, headache, episodic flushing, tachycardia, wheezing, colic, and diarrhea, are uncommon and occur most frequently in the more severe types of mastocytosis. Flushing is by far the most common symptom seen.

The second type of urticaria pigmentosa may begin in infancy but typically develops in adulthood. This type does not resolve, and new lesions continue to develop throughout life. It is associated with mutations in the stem cell factor gene. Patients with this type of mastocytosis are the population in whom systemic involvement may develop.

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**Telangiectasia macularis eruptiva perstans** is another variant that consists of telangiectatic hyperpigmented macules that are usually localized to the trunk. These lesions do not urticate when stroked. This form of the disease is seen primarily in adolescents and adults.

**Differential Diagnosis**

The differential diagnosis of solitary mastocytomas includes recurrent bullous impetigo, herpes simplex, congenital melanocytic nevi, and juvenile xanthogranuloma.

Urticaria pigmentosa can be confused with drug eruptions, postinflammatory pigmented change, juvenile xanthogranuloma, pigmented nevi, ephelides, xanthomas, chronic urticaria, insect bites, and bullous impetigo. Diffuse cutaneous mastocytoma may be confused with epidermolytic hyperkeratosis.

Telangiectasia macularis eruptiva perstans must be differentiated from other causes of telangiectasia.
Prognosis
Spontaneous involution occurs in all patients with solitary mastocytomas and classic infantile urticaria pigmentosa. The incidence of systemic manifestations in these patients is very low. The continued development of lesions past the age of 4 yr implies likely chronic disease with stem cell factor gene mutation and a higher risk for systemic involvement.

Treatment
Solitary mastocytomas usually do not require treatment. Lesions that blister may be treated with topical steroids following each blistering episode.

In urticaria pigmentosa, flushing can be precipitated by excessively hot baths, vigorous rubbing of the skin, and certain drugs, such as codeine, aspirin, morphine, atropine, ketorolac, alcohol, tubocurarine, iodine-containing radiographic dyes, and polymyxin B (Table 659-5). Avoidance of these triggering factors is advisable; it is notable that general anesthesia may be safely performed with appropriate precautions.

For patients who are symptomatic, oral antihistamines may be palliative. H1 receptor antagonists (hydroxyzine) are the initial drugs of choice for systemic signs of histamine release. If H1 antagonists are unsuccessful, H2 receptor antagonists may be helpful in controlling pruritus or gastric hypersecretion. Topical steroids are of benefit in controlling skin urtication and blistering. Oral mast cell–stabilizing agents, such as cromolyn sodium or ketotifen, may also be effective for diarrhea or abdominal cramping and some systemic symptoms such as headache or muscle pain.

For patients with diffuse cutaneous mastocytosis, the treatment is the same as for urticaria pigmentosa, although in early life. Phototherapy with narrow-band UV (UVB or UVA-1) or psoralen with UVA treatment may be required to control symptoms.

Lesions of telangiectasia macularis eruptiva perstans may be cautiously treated with vascular pulsed-dye lasers.

Bibliography is available at Expert Consult.
Bibliography
Diseases involving the subcutis are usually characterized by necrosis and/or inflammation; they may occur either as a primary event or as a secondary response to various stimuli or disease processes. The principal diagnostic criteria relate to the appearance and distribution of the lesions, associated symptoms, results of laboratory studies, histopathology, and natural history and exogenous provocative factors of these conditions.

**CORTICOSTEROID-INDUCED ATROPHY**

Intradermal or subcutaneous injection of a corticosteroid can produce deep atrophy accompanied by surface pigmented changes and telangiectasia (Fig. 660-1). These changes occur approximately 2-8 wks after injection and may last for months.

660.1 **Panniculitis and Erythema Nodosum**

Inflammation of fibrofatty subcutaneous tissue may primarily involve the fat lobule or, alternatively, the fibrous septum that compartmentalizes the fatty lobules. Lobular panniculitis that spares the subcutaneous vasculature includes poststeroid panniculitis, lupus erythematosus profundus, pancreatic panniculitis, $\alpha_1$-antitrypsin deficiency, subcutaneous fat necrosis of the newborn, sclerema neonatorum, cold panniculitis, subcutaneous sarcoidosis, and factitial panniculitis. Lobar panniculitis with vasculitis occurs in erythema induratum and, occasionally, as a feature of Crohn disease (see Chapter 336.2). Inflammation predominantly within the septum, sparing the vasculature, may be seen in erythema nodosum (Table 660-1 and Fig. 660-2), necrobiosis lipoidica, progressive systemic sclerosis (see Chapter 160), and subcutaneous granuloma annulare (see Chapter 659). Septal panniculitis that includes inflammation of the vessels is found primarily in leukocytoclastic vasculitis and polyarteritis nodosa (see Chapter 167).
ERYTHEMA NODOSUM
Etiology and Pathogenesis
The etiology is unknown in 30-50% of pediatric cases of erythema nodosum; Table 660-1 lists other etiologies. Most common etiologies in children include: group A streptococcal infection, Yersinia enterocolitica gastroenteritis, medications (cephalosporins, penicillins, macrolides), and inflammatory disorders (inflammatory bowel disease); sarcoidosis should be considered in young adults.

Clinical Manifestations
Erythema nodosum is a nodular, erythematous hypersensitivity reaction that typically appears with multiple lesions on the anterior surfaces of the arms and legs in the pretibial area (more common) and less often in other cutaneous areas containing subcutaneous fat. The lesions vary in size from 1-6 cm, are symmetric, and are oval with the longer axis parallel to the extremity. They initially appear bright or dull red but progress to a brown or purple; they are painful and usually do not ulcerate (see Fig. 660-2). Initial lesions may resolve in 1-2 wk, but new lesions may continue to appear for 2-6 wk. Repeat episodes may occur weeks to months later. Prior to or immediately at the onset of lesions, there may be systemic manifestations that include fever, malaise, arthralgias (50-90%) and rheumatoid factor negative arthritis.

Histology
A septal panniculitis with thickening of the septa with inflammatory cells infiltrate comprised of neutrophils acutely. Monocytes and histiocytes predominate in chronic erythema nodosum.

Treatment
Treatment includes that of the underlying disease as well as symptomatic relief with nonsteroidal antiinflammatory agents. Salicylates, supersaturated solution of potassium iodide (oral), colchicine, intraloskeletal injections of steroids and, in severe, persistent, or recurrent lesions, oral steroids have been employed. The idiopathic form is a self-limited disorder. Protracted or recurrent cases may warrant further workup including antistreptolysin O/deoxyribonuclease B, complete blood count, throat culture, purified protein derivative, QuantiFERON-TB gold assay, chest radiograph, erythrocyte sedimentation rate, and C-reactive protein.

POST-STEROID PANNICULITIS
Etiology and Pathogenesis
The mechanism of the inflammatory reaction in the fat in poststeroid panniculitis is unknown.

Clinical Manifestations
Majority of the cases of post-steroid panniculitis have been reported in children. The disorder occurs in children who have received high-dose corticosteroids. In 1-2 wk after discontinuation of the drug, multiple subcutaneous nodules usually appear on the cheeks, although other areas may be involved. Nodules range in size from 0.5-4.0 cm, are erythematous or skin colored, and may be pruritic or painful.

Histology
A lobular panniculitis with a mixed infiltrate of lymphocytes, histiocytes, and neutrophils is seen. Scattered swollen adipocytes with eosinophilic, needle-shaped crystals are also seen. The epidermis, dermis, and fibrous septa of the fat are normal. Vasculitis is not seen.

Treatment
Treatment of poststeroid panniculitis is unnecessary because the lesions remit spontaneously over a period of months without scarring.

LUPUS ERYTHEMATOSUS PROFUNDUS (LUPUS ERYTHEMATOSUS PANNICULITIS)
Etiology and Pathogenesis
It is unknown what separates those patients in whom lupus erythematosus profundus develops from other patients with systemic lupus erythematosus. This variant of chronic cutaneous lupus erythematosus is rare in childhood. Recent studies show only 2-5% of patients with lupus erythematosus profundus have associated systemic lupus erythematosus. Mean age of onset in reported pediatric cases is 9.8 yr.

Clinical Manifestations
Lupus erythematosus profundus manifests as 1 to several firm, tender, well-defined, purple plaques or nodules 1-3 cm in diameter. Majority of pediatric cases involve the face and proximal upper extremities. This condition may occur in patients with systemic or discoid lupus erythematosus and may precede or follow the development of other cutaneous lesions. The overlying skin is usually normal but may be erythematous, atrophic, poikilodermatous, or hyperkeratotic (Fig. 660-3). On healing, a shallow depression generally remains or, rarely, soft pink areas of anetoderma result.
Histology
The histopathologic changes in lupus erythematosus profundus are distinctive and may allow the clinician to make the diagnosis in the absence of other cutaneous lesions of lupus erythematosus. The panniculitis is characterized by a mostly nodular dense infiltrate of lymphocytes and plasma cells. Necrosis of the fat lobule is characteristic. A dense perivascular and periappendiceal lymphocytic infiltrate is seen in the dermis. Lichenoid changes may be identified at the epidermal–dermal junction. Histopathologic differentiation from subcutaneous panniculitis–like T-cell lymphoma may be difficult. Results of lupus band and antinuclear antibody tests are usually positive.

Treatment
Nodules tend to be persistent and frequently ulcerate. Long-term follow-up for possible systemic involvement is warranted. There is no consensus on the utility of laboratory testing. Antinuclear antibody is positive in only a small subset of patients. Few case reports show slight neutropenia, leukopenia, and mildly elevated liver function tests. Hydroxychloroquine (2–5 mg/kg/day) is the treatment of choice for lupus erythematosus profundus. Intralosional corticosteroids may worsen the residual lipoatrophy. Immunosuppressive agents are indicated only for treatment of other severe manifestations of systemic lupus erythematosus. Avoidance of sun exposure and trauma is also important.

α1-Antitrypsin Deficiency
Etiology and Pathogenesis
Individuals with α1-antitrypsin deficiency have severe homozygous deficiency or, rarely, a partial deficiency of the protease inhibitor α1-antitrypsin, which inhibits trypsin activity and the activity of elastase, serine proteases, collagenase, factor VIII, and kallikrein (see Chapter 393). Panniculitis occurs with severe α1-antitrypsin deficiency or the Z subtype.

Clinical Manifestations
Cellulitis-like areas or tender, red nodules occur on the trunk or proximal extremities (see Chapter 393). Nodules tend to ulcerate spontaneously and discharge an oily yellow fluid. Panniculitis may be associated with other manifestations of the disease, such as panacinar emphysema, noninfectious hepatitis, cirrhosis, persistent cutaneous vasculitis, cold contact urticaria, and acquired angioedema. Diagnosis can be substantiated by a decreased level of serum α1-antitrypsin activity.

Histology
Extensive septal and lobular neutrophilic infiltrate with necrosis of the fat is observed.

Figure 660-3 Deep nodule of lupus profundus with overlying hyperkeratotic lesion of discoid lupus erythematosus.

Pancreatic Panniculitis
Etiology and Pathogenesis
Pathogenesis of pancreatic panniculitis appears to be multifactorial, involving liberation of the lipolytic enzymes lipase, trypsin, and amylase into the circulation, causing adipocyte membrane damage and intracellular lipolysis. There is no correlation, however, between the occurrence of panniculitis and the serum concentration of pancreatic enzymes.

Clinical Manifestations
Pancreatic panniculitis manifests most commonly on the preordial regions, thighs, or buttocks as tender, erythematous nodules that may be fluctuant and occasionally discharge an oily yellowish substance. It appears most often in males with alcoholism but may also occur in patients with pancreatitis as a result of cholelithiasis or abdominal trauma, with rupture of a pancreatic pseudocyst, with pancreatic ductal adenocarcinoma, or with pancreatic acinar cell carcinoma. Associated features may include polyarthritis (pancreatitis-panniculitis-polyarthritis syndrome). In almost 65% of patients, abdominal signs are absent or mild, making the diagnosis difficult.

Histology
Microscopic changes consist of multiple foci of fat necrosis that contain ghost cells with thick, shadowy walls and no nuclei. A polymorphous inflammatory infiltrate surrounds the areas of fat necrosis.

Treatment
The primary pancreatic disorder must be treated. The arthritis may be chronic and responds poorly to treatment with nonsteroidal antiinflammatory drugs and oral corticosteroids.

Subcutaneous Fat Necrosis
Etiology and Pathogenesis
The cause of subcutaneous fat necrosis (SCFN) is unknown. The disease in infants may be a result of ischemic injury from various perinatal complications, such as maternal preeclampsia, birth trauma, asphyxia, and prolonged hypothermia. Whole-body cooling for neonatal encephalopathy is increasingly associated with SCFN. Susceptibility is attributed to differences in composition between the subcutaneous tissue of young infants and that of older infants, children, and adults. Neonatal fat solidifies at a relatively high temperature because of its relatively greater concentration of high-melting-point saturated fatty acids, such as palmitic and stearic acids.

Clinical Manifestations
This inflammatory disorder of adipose tissue occurs primarily in the 1st 4 wk of life in full-term or postterm infants. Typical lesions are asymptomatic, indurated, erythematous to violaceous, sharply demarcated plaques or nodules on the cheeks, buttocks, back, thighs, or upper arms (Fig. 660-4). Lesions may be focal or extensive and are generally asymptomatic, although they may be tender during the acute phase. Uncomplicated lesions involute spontaneously within weeks to months, usually without scarring or atrophy. Calcium deposition may occasionally occur within areas of fat necrosis, which may sometimes result in rupture and drainage of liquid material. These areas may heal with atrophy. A rare but potentially life-threatening complication is hypercalcemia. It manifests at 1-6 mo of age (in a review of 20 cases, average age at onset was 6.7 wk) as lethargy, poor feeding, vomiting, failure to thrive, irritability, seizures, shortening of the QT interval on electrocardiography, or renal failure. The origin of the hypercalcemia is unknown, but an accepted hypothesis is that the macrophages present produce 1,25-dihydroxyvitamin D3 which, in turn, increases calcium uptake. Infants with SCFN should be followed for several months to monitor for delayed hypercalcemia.
Sclerema neonatorum is almost always associated with serious illness, such as sepsis, congenital heart disease, multiple congenital anomalies, or hypothermia. The appearance of sclerema in a sick infant should be regarded as an ominous prognostic sign. The outcome depends on the response of the underlying disorder to treatment.

COLD PANNICULITIS
Etiology and Pathogenesis
The pathogenic mechanism of cold panniculitis may be similar to that of SCFN, involving a greater propensity of fat to solidify in infants than in older children and adults as a result of the higher percentage of saturated fatty acids in the subcutaneous fat of infants. Lesions occur in infants after prolonged cold exposure, especially on the cheeks, or after prolonged application of a cold object such as an ice cube, ice bag, or fruit ice pop to any area of the skin.

Clinical Manifestations
Ill-defined, erythematous to bluish, indurated plaques or nodules arise within hours to a couple days of exposure on exposed surfaces (face, arms, legs), persist for 2-3 wk, and heal without residua.

Histology
Histopathologic examination reveals an infiltrate of lymphoid and histiocytic cells around blood vessels at the dermal–subdermal junction and in the fat lobules; by the 3rd day, some of the fat cells in the subcutis may have ruptured and coalesced into cystic structures.

Differential Diagnosis
Cold panniculitis may be confused with facial cellulitis caused by Haemophilus influenzae type b. Unlike in buccal cellulitis, the area may be cold to the touch, and the patient is afebrile and appears well.

Treatment
Treatment is unnecessary because cold panniculitis spontaneously resolves. Recurrence of the lesions is common, emphasizing the importance of parental education in treating affected patients.

CHILBLAINS (PERNIO)
Etiology and Pathogenesis
Vasospasm of arterioles from damp cold exposure with resultant hypoxemia and localized perivascular mononuclear inflammation appears to be responsible for chilblains. The disease is associated with cryoglobulins, lupus erythematosus with antiphospholipid antibodies, anorexia nervosa, and thin body habitus.

Clinical Manifestations
The condition is characterized by localized symmetric erythematous to purplish edematous plaques and nodules in areas exposed to cold, typically acral areas (distal hands and feet, ears, face; see Chapter 76). Lesions develop 12-24 hr after cold exposure and may be associated with itching, burning, or pain. Blister formation and ulceration are rare.

Histology
Histopathologic examination reveals marked dermal edema and a perivascular and periappendiceal, predominantly T-cell lymphocytic infiltrate in the papillary and reticular dermis.

Differential Diagnosis
Raynaud phenomenon is more acute in nature than chilblains, with characteristic color changes and no chronic lesions. Frostbite due to extreme cold exposure is painful and involves freezing of the tissue with resultant tissue necrosis.

Treatment
Most cases of chilblains resolve spontaneously but can last 2-3 wk. Prevention is the treatment of choice. Nifedipine (0.25-0.5 mg/kg tid,
maximum 10 mg/dose) may be used in severe cases. Unusual or persistent cases of panniculitis in children may warrant further work-up including antinuclear antibody titer, cryoglobulins, complete blood count, and cold agglutinins.

**FACTITIAL PANNICULITIS**

**Étiology and Pathogenesis**

Factitial panniculitis results from subcutaneous injection by the patient or a proxy of a foreign substance, the most common types of which are organic materials, such as milk and feces; drugs, such as the opiates and pentazocine; oily materials, such as mineral oil and paraffin; and the synthetic polymer povidone.

**Clinical Manifestations**

Indurated plaques, ulcers, or nodules that liquefy and drain may be noted clinically in factitial panniculitis.

**Histology**

The histopathology is variable, depending on the injected substance, but may include the presence of birefringent crystals, oil cysts surrounded by fibrosis and inflammation, and an acute inflammatory reaction with fat necrosis. Vessels are characteristically spared.

**Treatment**

Treatment of factitial panniculitis must address the primary reason the patient is performing the self-destructive act. Munchhausen syndrome by proxy should be considered in young children.

**Bibliography is available at Expert Consult.**

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### 660.2 Lipodystrophy

**JiaDe Yu**

Several rare conditions are associated with loss of fatty tissue in a partial or generalized distribution and can be familial or acquired. Loss of adipose tissue at certain sites is often accompanied by fat redistribution and consequent hypertrophy of adipose at other sites. Extent of fatty tissue loss or expansion correlates with the degree of clinical and metabolic abnormalities.

**PARTIAL LIPODYSTROPHY**

Partial lipodystrophy may be familial or acquired. Loss of adipose tissue is not preceded by an inflammatory phase, and histopathologic examination reveals only absence of subcutaneous fat. There are 5 forms of familial partial lipodystrophy (FPLD):

- **Type 1** (FPLD1–Kobberling) is characterized by loss of adipose tissue confined to the extremities and gluteal region. Fat distribution of the face, neck, and trunk may be normal or increased. Hyperlipidemia, insulin-resistant diabetes mellitus, and eruptive xanthomas may be seen. The gene is unknown, but only females are affected.
- **Type 2** (FPLD2–Dunnigan) is the most common form of FPLD and caused by mutations in the laminin A/C gene leading to premature death of adipocytes. Fat distribution is normal in childhood, but atrophy commences with puberty. Lipodystrophy is seen in the trunk, gluteal region, and extremities. Adipose tissue accumulates in the face and neck and may also be seen in the axillae, back, labia majora, and infraabdominal region. Insulin-resistant diabetes mellitus and hypertriglyceridemia develop, but high-density lipoprotein and cholesterol levels are low. Both males and females are affected, but the diagnosis may be more difficult in males owing to body habitus.
- **Type 3** (FPLD3) is caused by mutations in the peroxisome proliferation–activated receptor γ (PPARG) gene inhibiting adipocyte differentiation. Lipodystrophy is seen in the distal limbs and gluteal region. Insulin-resistant diabetes mellitus, primary amenorrhea, acanthosis nigricans, hypertension, and fatty infiltration of the liver are present.
- **Type 4** (FPLD4) and **Type 5** (FPLD5) are caused by mutations in AKT2 and Perilipin-1 (PLIN1), respectively. Both types are also characterized by loss of subcutaneous fat primarily from the extremities.

**Acquired partial lipodystrophy** (Barraquer-Simons syndrome) is caused by mutations in the LMNB2 gene. Females are more commonly affected. Fat loss begins in childhood or adolescence and progresses in a cephalotruncal direction, beginning on the face and sparing the lower extremities. Excess fat deposition is seen in the hips and legs, especially in females. Low levels of complement C3 are almost universally seen because of the presence of C3 nephritic factor that stabilizes C3 convertase, allowing for unopposed activation of the alternate complement pathway leading to decreased level of C3. Membranous proliferative glomerulonephritis and other autoimmune diseases may develop. Insulin-resistant diabetes mellitus is rare.

**GENERALIZED LIPODYSTROPHY**

Generalized lipodystrophy may also be congenital or acquired. Congenital generalized lipodystrophy is seen in 4 forms:

- **Type 1** (Berardinelli-Seip congenital lipodystrophy type 1 [BSCL1]) is an autosomal recessive disorder caused by mutations in the 1-acetylgluceral-3-phosphate-O-acetyltransferase (AGPAT2) gene.
- **Type 2** (Berardinelli-Seip congenital lipodystrophy type 2 [BSCL2]) is also autosomal recessive and caused by mutations in the seipin gene.
- **Type 3** (CAV1) is autosomal recessive and caused by mutations in the caveolin 1 gene.
- **Type 4** (PTRL) is autosomal recessive and caused by mutations in the polymerase I and transcript release factor gene. In addition to the classic phenotype of congenital generalized lipodystrophy, these patients also have muscular dystrophy and cardiac conduction abnormalities (QT prolongation).

Marked lipodystrophy occurs at birth or in early infancy with prominent muscularity. Diabetes mellitus, hypertriglyceridemia, hepatic steatosis, acanthosis nigricans, and muscular hypertrophy occur. Congenital generalized lipodystrophy type 1 and type 2 are the most common, with the latter having a more severe phenotype characterized by extensive fat loss, cardiomyopathy, intellectual impairment, and premature death in ~15% of cases.

**Acquired generalized lipodystrophy** is more common in females. The most common associated disorder is juvenile dermatomyositis (78%). Panniculitis preceding the loss of fat is seen in 17% of affected individuals. More than half of the children may have other complications, including acanthosis nigricans, hyperpigmentation, hepatomegaly, hypertension, protuberant abdomen, and hyperlipidemia.

**Localized lipoatrophy** can be idiopathic or secondary to subcutaneous medication injections, pressure, and panniculitis. Unlike generalized or partial lipodystrophy, localized lipoatrophy involves a small part of the body and have no accompanying metabolic derangements. Idiopathic localized lipoatrophy manifests as annular atrophy at the ankles; a bandlike semicircular depression 2–4 cm in diameter on the thighs, abdomen, and/or upper groin or as a centrifugally spreading, depressed, bluish plaque with an erythematous margin. **Insulin lipoatroph**y usually occur approximately 6 mo to 2 yr after initiation of relatively high doses of insulin. A dimple or well-circumscribed depression at or surrounding the site of injection is typically seen. Biopsy reveals a marked decrease or absence of subcutaneous tissue, without inflammation or fibrosis. In some patients, hypertrophy occurs clinically. In these cases, the mid-dermal collagen is replaced by hypertrophic fat cells on histopathologic sections. A recent study shows that adipocytes chronically exposed to high insulin concentrations become insulin-resistant, leading to lipolysis and atrophy. Lesions may also be prevented by frequent alteration of injection sites.

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


Bibliography


Eccrine glands are found over nearly the entire skin surface and provide the primary means, through evaporation of the water in sweat, of cooling the body. These glands have no anatomic relationship to hair follicles and secrete a relatively large amount of odorless aqueous sweat. In contrast, apocrine sweat glands are limited in distribution to the axillae, anogenital skin, mammary glands, ceruminous glands of the ear, Moll glands in the eyelid, and selected areas of the face and scalp. Each apocrine gland duct enters the pilosebaceous follicle at the level of the infundibulum and secretes a small amount of a complex, viscous fluid that, on alteration by microorganisms, produces a distinctive body odor. Some disorders of these 2 types of sweat glands are similar pathogenetically, whereas others are unique to a given gland.

ANHIDROSIS

 Neuropathic anhidrosis results from a disturbance in the neural pathway from the control center in the brain to the peripheral efferent nerve fibers that activate sweating. Disorders in this category, which are characterized by generalized anhidrosis, include tumors of the hypothalamus and damage to the floor of the third ventricle. Pontine or medullary lesions may produce anhidrosis of the ipsilateral face or neck and ipsilateral or contralateral anhidrosis of the rest of the body. Peripheral or segmental neuropathies, caused by leprosy, amyloidosis, diabetes mellitus, alcoholic neuritis, or syringomyelia, may be associated with anhidrosis of the innervated skin. Various autonomic disorders are also associated with altered eccrine sweat gland function.

At the level of the sweat gland, anticholinergics (drugs such as atropine and scopolamine) may paralyze the sweat glands. Acute intoxication with barbiturates or diazepam has produced necrosis of sweat glands, resulting in anhidrosis with or without erythema and bullae. Eccrine glands are largely absent throughout the skin or are present in a localized area among patients with hypohidrotic ectodermal dysplasia or localized congenital absence of sweat glands, respectively. Infiltrative or destructive disorders that may produce atrophy of sweat glands by pressure or scarring include scleroderma, acrodermatitis chronic a trophicans, radiodermatitis, burns, Stjøgren syndrome, multiple myeloma, and lymphoma. Obstruction of sweat glands may occur in miliaria and in a number of inflammatory and hyperkeratotic disorders, such as the ichthyoses, psoriasis, lichen planus, pemphigus, pachyonychia congenita, atop eczematous dermatitis, and seborrheic dermatitis. Occlusion of the sweat pore may also occur with the topical agents aluminum and zirconium salts, formaldehyde, or glutaraldehyde.

Diverse disorders that are associated with anhidrosis by unknown mechanisms include dehydration; toxic overdose with lead, arsenic, thallium, fluorine, or morphine; uremia; cirrhosis; endocrine disorders such as Addison disease, diabetes mellitus, diabetes insipidus, and hyperthyroidism; and inherited conditions such as autonomic neuropathies, Fabry disease, Franceschetti-Jadassohn syndrome, which combines features of incontinentia pigmenti and hypohidrotic ectodermal dysplasia, congenital insensitivity to pain with anhidrosis syndrome, and familial anhidrosis with neural labyrinthitis.

Anhidrosis may be complete, but in many cases, what appears clinically to be anhidrosis is actually hypohidrosis caused by anhidrosis of many, but not all, eccrine glands. Compensatory, localized hyperhidrosis of the remaining functional sweat glands may occur, particularly in diabetes mellitus and miliaria. The primary complication of anhidrosis is hyperthermia, seen primarily in anhidrotic ectodermal dysplasia or in otherwise normal preterm or full-term neonates who have immature eccrine glands.

HYPERHIDROSIS

Etiology and Pathogenesis

Hyperhidrosis is excessive sweating beyond what is physiologically necessary for temperature control and occurs in 3% of the population with about half having axillary hyperhidrosis. The numerous disorders that may be associated with increased production of eccrine sweat may also be classified into those with neural mechanisms involving an abnormality in the pathway from the neural regulatory centers to the sweat gland and those that are nonneurally mediated and occur by direct effects on the sweat glands (Table 661-1).

Clinical Manifestations

The average age at onset of hyperhidrosis is 14-25 yr. The excess sweating may be continuous or may occur in response to emotional stimuli. In severe cases, sweat may be seen to drip constantly from the hands.

Treatment

Excessive sweating of the palms and soles (volar hyperhidrosis) and axillary sweating may respond to 20% aluminum chloride in anhydrous ethanol applied under occlusion for several hours, iontophoresis, injection with botulinum toxin, therapy with oral anticholinergics, or in severe, refractory cases, cervicothoracic or lumbar sympathectomy. Reports of successful treatment of hyperhidrosis with microwave technology are available, but studies are faulted with small sample size and lack of controls.

### Table 661-1 Causes of Hyperhidrosis

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### Table 661-1

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MILIARIA

Etiology and Pathogenesis
Miliaria results from retention of sweat in occluded eccrine sweat ducts. The keratinous plug does not form until the later stages of the disease and therefore does not appear to be the primary cause of the sweat duct obstruction. The initial obstruction is postulated to be caused by swelling of the ductal epidermal cells, perhaps from inhibition of water. Retrograde pressure may result in rupture of the duct and leakage of sweat into the epidermis and/or the dermis. The eruption is most often induced by hot, humid weather, but it may also be caused by high fever. Infants who are dressed too warmly may demonstrate this eruption indoors, even during the winter.

Clinical Manifestations
In miliaria crystallina, asymptomatic, noninflammatory, pinpoint, clear vesicles may suddenly erupt in profusion over large areas of the body surface, leaving brawny desquamation on healing (Fig. 661-1). This type of miliaria occurs most frequently in newborn infants because of the relative immaturity and delayed patency of the sweat duct and the tendency for infants to be nursed in relatively warm, humid conditions. It may also occur in older patients with hyperpyrexia.

Miliaria rubra is a less superficial eruption characterized by erythematous, minute papulovesicles that may impart a prickling sensation. The lesions are usually localized to sites of occlusion or to flexural areas, such as the neck, groin, and axillae, where friction may have a role in their pathogenesis. Involved skin may become macerated and eroded. Lesions of miliaria rubra, however, are extrafollicular.

Repeated attacks of miliaria rubra may lead to miliaria profunda, which is caused by rupture of the sweat duct deeper in the skin, at the level of the dermal–epidermal junction. Severe, extensive miliaria rubra or miliaria profunda may result in disturbance of heat regulation. Lesions of miliaria rubra may become infected, particularly in malnourished or debilitated infants, leading to development of periporitis staphylogenesis, which involves extension of the process from the sweat duct into the sweat gland.

Histology
Histologically, miliaria crystallina reveals an intracorneal or subcorneal vesicle in communication with the sweat duct, whereas in miliaria rubra, one sees focal areas of spongiosis and spongotic vesicle formation in close proximity to sweat ducts that generally contain a keratinous plug.

Differential Diagnosis
The clarity of the fluid, superficiality of the vesicles, and absence of inflammation permit differentiation of miliaria crystallina from other blistering disorders. Miliaria rubra may be confused with or superimposed on other diaper area eruptions, including candidosis and folliculitis.

Treatment
All forms of miliaria respond dramatically to cooling of the patient by regulation of environmental temperatures and by removal of excessive clothing; administration of antipyretics is also beneficial to patients with fever. Topical agents are usually ineffective and may exacerbate the eruption.

BROMHIDROSIS

The excessive odor that characterizes bromhidrosis may result from alteration of either apocrine or eccrine sweat. Apocrine bromhidrosis develops after puberty as a result of the formation of short-chain fatty acids and ammonia by the action of anaerobic diphtheroids on axillary apocrine sweat. Eccrine bromhidrosis is caused by microbiologic degradation of stratum corneum that has become softened by excessive eccrine sweat. The soles of the feet and the intertriginous areas are the primary affected sites. Hyperhidrosis, warm weather, obesity, intertrigo, and diabetes mellitus are predisposing factors. Treatments that may be helpful include cleansing with germicidal soaps, topical clindamycin or erythromycin, or topical application of aluminum or zirconium. Treatment of any associated hyperhidrosis is mandatory.

HIDRADENITIS SUPPURATIVA

Etiology and Pathogenesis
Hidradenitis suppurativa is a disease of the apocrine gland–bearing areas of the skin. Pathogenesis of hidradenitis suppurativa is controversial. It is believed that it is a primary inflammatory disorder of the hair follicle and not solely an alteration of apocrine glands. It is considered a part of the follicular occlusion tetrad, along with acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus. The natural history of the disease involves progressive dilation below the follicular obstruction, leading to rupture of the duct, inflammation, sinus tract formation, and destructive scarring.

Clinical Manifestations
Hidradenitis suppurativa is a chronic, inflammatory, supplicative disorder of the follicular units in the axillae, the anogenital area, and, occasionally, the scalp, posterior aspect of the ears, female breasts, and periumbilical area. Onset of clinical manifestations is sometimes preceded by pruritus or discomfort and usually occurs during puberty or early adulthood. Solitary or multiple painful erythematous nodules, deep abscesses, and contracted scars are sharply confined to areas of skin containing apocrine glands. When the disease is severe and chronic, sinus tracts, ulcers, and thick, linear fibrotic bands develop. Hidradenitis suppurativa tends to persist for many years, punctuated by relapses and partial remissions. Complications include cellulitis, ulceration, and burrowing abscesses that may perforate adjacent structures, forming fistulas to the urethra, bladder, rectum, or peritoneum. Episodic inflammatory arthritis develops in some patients.

Histology
Early lesions are characterized by a keratinous plug in the apocrine duct or hair follicle orifice and by cystic distention of the follicle. The process generally but not necessarily extends into the apocrine gland. Later changes include inflammation within and around apocrine glands. Scarring may obliterate skin appendages.

Differential Diagnosis
Early lesions of hidradenitis suppurativa are often mistaken for infected epidermal cysts, furuncles, scrofuloderma, actinomycosis, cat-scratch disease, granuloma inguinale, or lymphogranuloma venereum. Sharp localization to areas of the body that bear apocrine glands, however, should suggest hidradenitis. When involvement is limited to the anogenital region, the condition may be difficult to distinguish from Crohn disease.

Treatment
Conservative management includes cessation of smoking, weight loss, and avoidance of irritation of the affected area. Warm compresses and topical antiseptic or antibacterial soaps may also be helpful. For mild,
early disease, topical clindamycin 1% may be helpful. For more-severe
disease, therapy may be initiated with doxycycline (100 mg bid) or
minocycline (100 mg bid). Some patients require intermittent or long-
term antibiotic treatment. Combination therapy with clindamycin and
rifampin is helpful in some patients. Oral retinoids (1 mg/kg/day) for
5-6 mo may also be effective. Oral contraceptive agents, which contain
a high estrogen : progesterone ratio and low androgenicity of the pro-
gesterone, are another alternative. Laser hair ablation has proven
helpful in some studies as well. Systemic immunosuppressants (inflix-
imab, adalimumab, cyclosporine) and medications targeted at glucose
metabolism and the metabolic syndrome (metformin) have been
helpful. Surgical measures may be required for control or cure, espe-
cially in localized, recalcitrant cases.

**FOX-FORDYCE DISEASE**

**Etiology and Pathogenesis**
The cause of Fox-Fordyce disease is unknown.

**Clinical Manifestations**
This disease is most common in females and manifests during puberty
to the 3rd decade of life as pruritus in the axillae. Pruritus is exacer-
bated by emotional stress and stimuli that induce apocrine sweating.
Dome-shaped, skin-colored to slightly hyperpigmented, follicular
papules develop in the pruritic areas.

**Histology**
Histopathologically, one sees keratinous plugging of the distal apocrine
duct, rupture of the intraepidermal portion of the apocrine duct, peri-
ductal microvesicle formation, and periductal acanthosis.

**Treatment**
Fox-Fordyce disease is difficult to treat. Oral contraceptive pills and
topical corticosteroids or retinoic acid may help some patients.

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


Disorders of hair in infants and children may be a result of intrinsic disturbances of hair growth, underlying biochemical or metabolic defects, inflammatory dermatoses, or structural anomalies of the hair shaft. Excessive and abnormal hair growth is referred to as hypertrichosis or hirsutism. Hypertrichosis is excessive hair growth at inappropriate locations; hirsutism is an androgen-dependent male pattern of hair growth in women. Hypotrichosis is deficient hair growth. Hair loss, partial or complete, is called alopecia. Alopecia may be classified as nonscarring or scarring; the latter type is rare in children and, if present, is most often caused by prolonged or untreated inflammatory conditions, such as pyoderma and tinea capitis.

**HYPERTRICHOSIS**

Hypertrichosis is rare in children and may be localized or generalized and permanent or transient. Table 662-1 lists some of the many causes of hypertrichosis.

**HYPOTRICHOSIS AND ALOPECIA**

Table 662-2 lists some of the disorders associated with hypotrichosis and alopecia. True alopecia is rarely congenital; it is more often related to environmental factors or systemic diseases.
Disorders of Hair

Any inflammatory condition of the scalp, such as atopic dermatitis or seborrheic dermatitis, if severe enough, may result in partial alopecia; hair growth returns to normal if the underlying condition is treated successfully, unless the hair follicle has been permanently damaged.

Hair loss in childhood should be divided into the following 4 categories: congenital diffuse, congenital localized, acquired diffuse, and acquired localized.

Acquired localized hair loss is the most common type of hair loss seen in childhood. Three conditions—traumatic alopecia, alopecia areata, tinea capitis—are predominantly seen (Tables 662-3 and 662-4).

**TRAUMATIC ALOPECIA (TRACTION ALOPECIA, HAIR PULLING, TRICHOTILLOMANIA)**

**Traction Alopecia**

Traction alopecia is common and is seen in almost 20% of African-American schoolgirls. It is caused by trauma to hair follicles from tight braids or ponytails, headbands, rubber bands, curlers, or rollers (Fig. 662-1). There is a greater risk of traction alopecia if hair trauma is combined with chemically relaxed hair. Broken hairs and inflammatory follicular papules in circumscribed patches at the scalp margins are characteristic and may be subtended by regional lymphadenopathy. Children and parents must be encouraged to avoid devices that cause trauma to the hair and, if necessary, to alter the hairstyle. Otherwise, scarring of hair follicles may occur.

**Hair Pulling**

Hair pulling in childhood is usually an acute reactionary process related to emotional stress or a habit (especially in young children). It may also be seen in trichotillomania (obsessive–compulsive disorder) and as part of more severe psychiatric disorders usually in adolescents.

**Trichotillomania**

**Etiology and Pathogenesis.** The diagnostic criteria for trichotillomania include visible hair loss attributable to pulling; mounting tension preceding hair pulling; gratification or release of tension after hair pulling; and absence of hair pulling attributable to hallucinations, delusions, or an inflammatory skin condition.

**Clinical Manifestations.** Compulsive pulling, twisting, and breaking of hair produces irregular areas of incomplete hair loss, most often on the crown and in the occipital and parietal areas of the scalp. Occasionally, eyebrows, eyelashes, and body hair are traumatized. Some plaques of alopecia may have a linear outline. The hairs remaining within the areas of loss are of various lengths (Fig. 662-2) and are typically blunt-tipped because of breakage. The scalp usually appears normal, although hemorrhage, crusting (Fig. 662-3), and chronic folliculitis may also occur. Trichophagy, resulting in trichobezoars, may complicate this disorder.

**Differential Diagnosis.** Acute reactional hair pulling, tinea capitis, and alopecia areata must be considered in the differential diagnosis of trichotillomania (see Tables 662-3 and 662-4).

**Histology.** Histologic changes include coexistent normal and damaged follicles, perifollicular hemorrhage, atrophy of some follicles, and catagen transformation of hair. In late stages, perifollicular fibrosis may occur. Long-term repeated trauma may result in irreversible damage and permanent alopecia.
Part XXXI ♦ The Skin

The Skin and vitiligo may also be seen. An increased incidence of alopecia areata has been reported in patients with Down syndrome (5-10%).

Differential Diagnosis
Tinea capitis, seborrheic dermatitis, trichotillomania, traumatic alopecia, and lupus erythematosus should be considered in the differential diagnosis of alopecia areata (see Tables 662-3 and 662-4).

 Alopecia areata is a T-cell driven autoimmune disorder producing nonscarring alopecia. The cause is unknown. It is hypothesized that in genetically susceptible individuals, loss of immune privilege of the hair follicle allows for T-cell inflammation against anagen hairs, follicles, leading to stoppage of hair growth.

Clinical Manifestations
Alopecia areata is characterized by rapid and complete loss of hair in round or oval patches on the scalp (Fig. 662-4) and on other body sites. In alopecia totalis, all the scalp hair is lost (Fig. 662-5); alopecia universalis involves all body and scalp hair. The lifetime incidence of alopecia areata is 0.1-0.2% of the population. More than half of affected patients are younger than 20 yr.

The skin within the plaques of hair loss appears normal. Alopecia areata is associated with atopy and with nail changes such as pits (Fig. 662-6), longitudinal striations, and leukonychia. Autoimmune diseases such as Hashimoto thyroiditis, Addison disease, pernicious anemia, ulcerative colitis, myasthenia gravis, collagen vascular diseases,

and vitiligo may also be seen. An increased incidence of alopecia areata has been reported in patients with Down syndrome (5-10%).

Differential Diagnosis
Tinea capitis, seborrheic dermatitis, trichotillomania, traumatic alopecia, and lupus erythematosus should be considered in the differential diagnosis of alopecia areata (see Tables 662-3 and 662-4).
Histology
A perifollicular infiltrate of inflammatory round cells is found in biopsy specimens from active areas of alopecia areata.

Treatment
The course is unpredictable, but spontaneous resolution in 6–12 mo is usual, particularly when relatively small, stable patches of alopecia are present. Recurrences are common. Onset at a young age, extensive or prolonged hair loss, and numerous episodes are usually poor prognostic signs. Alopecia universalis, alopecia totalis, and alopecia ophiasis (Fig. 662-7)—a type of alopecia areata in which hair loss is circumferential—are also less likely to resolve. Therapy is difficult to evaluate because the course is erratic and unpredictable. The use of high- or superpotency topical corticosteroids is effective in some patients. Intradermal injections of steroid (triamcinolone 5 mg/mL) every 4–6 wk may also stimulate hair growth locally, but this mode of treatment is impractical in young children or in patients with extensive hair loss. Systemic corticosteroid therapy (prednisone 1 mg/kg/day) is associated with good results; the permanence of cure is questionable, however, and the side effects of chronic oral corticosteroids are a serious deterrent. Some patients may maintain hair growth by switching to a more appropriate long-term immunosuppressant such as methotrexate. Additional therapies that are sometimes effective include short-contact anthralin, topical minoxidil, and contact sensitization with squaric acid dibutylester or diphencyprone. In general, parents and patients can be reassured that spontaneous remission of alopecia areata usually occurs. New hair growth may initially be of finer caliber and lighter color, but replacement by normal terminal hair can be expected.

ACQUIRED DIFFUSE HAIR LOSS
Telogen Effluvium
Telogen effluvium manifests as sudden loss of large amounts of hair, often with brushing, combing, and washing of hair. Diffuse loss of scalp hair occurs from premature conversion of growing, or anagen, hairs, which normally constitute 80–90% of hairs, to resting, or telogen, hairs. Hair loss is noted 6 wk to 3 mo after the precipitating cause, which may include childbirth; a febrile episode; surgery; acute blood loss, including blood donation; sudden severe weight loss; discontinuation of high-dose corticosteroids or oral contraceptives; and psychiatric stress. Telogen effluvium also accounts for the loss of hair by infants in the 1st few mo of life; friction from bed sheets, particularly in infants with pruritic, atopic skin, may exacerbate the problem. There is no inflammatory reaction; the hair follicles remain intact, and telogen bulbs can be demonstrated microscopically on shed hairs. Because >50% of the scalp hair is rarely involved, alopecia is usually not severe. Parents should be reassured that normal hair growth will return within approximately 3–6 mo.

Toxic Alopecia (Anagen Effluvium)
Anagen effluvium is an acute, severe, diffuse inhibition of growth of anagen follicles, resulting in loss of >80–90% of scalp hair. Hairs become dystrophic, and the hair shaft breaks at the narrowed segment. Loss is diffuse, rapid (1–3 wk after treatment), and temporary, as regrowth occurs after the offending agent is discontinued. Causes of anagen effluvium include radiation; cancer chemotherapeutic agents such as anti-metabolites, alkylating agents, and mitotic inhibitors; thallium; thiouracil; heparin; the coumarins; boric acid; and hypervitaminosis A.

CONGENITAL DIFFUSE HAIR LOSS
Congenital diffuse hair loss is defined as congenitally thin hair diffusely related to either hypoplasia of hair follicles or to structural defects in hair shafts.

Structural Defects of Hair
Structural defects of the hair shaft may be congenital, reflect known biochemical aberrations, or relate to damaging grooming practices. All the defects can be demonstrated by microscopic examination of affected hairs, particularly with scanning and transmission electron microscopy, though many can even be seen by simple trichogram done in the office.

Trichorrhexis Nodosa
Congenital trichorrhexis nodosa is an autosomal dominant condition. The hair is dry, brittle, and lusterless, with irregularly spaced grayish white nodes on the hair shaft. Microscopically, the nodes have the appearance of two interlocking brushes (Fig. 662-BA). The defect results from a fracture of the hair shaft at the nodal points caused by disruption of the cells in the hair cortex. Trichorrhexis nodosa has also been observed in some infants with Menkes syndrome, trichothiodystrophy, citrullinemia, and argininosuccinic aciduria.

Acquired Trichorrhexis Nodosa
Acquired trichorrhexis nodosa, the most common cause of hair breakage, occurs in 2 forms. Proximal defects are found most frequently in African-American children, whose complaint is not of alopecia but of failure of the hair to grow. The hair is short, and longitudinal splits, knots, and whitish nodules can be demonstrated in hair mounts. Easy breakage is demonstrated by gentle traction on the hair shafts. A history of other affected family members may be obtained. The problem may be caused by a combination of genetic predisposition and the cumulative mechanical trauma of rough combing and brushing, hair-straightening procedures, and "permanents." Patients must be cautioned to avoid damaging grooming techniques. A soft, natural-bristle brush and a wide-toothed comb should be used. The condition is self-limited, with resolution in 2–4 yr, if patients avoid damaging practices. Distal trichorrhexis nodosa is seen more frequently in white and Asian children. The distal portion of the hair shaft is thinned, ragged, and faded; white specks, sometimes mistaken for nits, may be noted along the shaft. Hair mounts reveal the paintbrush defect and the sites of excessive fragility and breakage. Localized areas of the moustache or beard may also be affected. Avoidance of traumatic grooming, regular trimming of affected ends, and the use of cream rinses to lessen tangling ameliorate this condition.

Pili Torti
Patients with pili torti present with spangled, brittle, coarse hair of different lengths over the entire scalp. There is a structural defect in which the hair shaft is grooved and flattened at irregular intervals and is twisted on its axis to various degrees. Minor twists that occur in normal hair should not be misconstrued as pili torti. Curvature of the hair follicle apparently leads to the flattening and rotation of the hair shaft. The genetic defect in isolated pili torti is unknown, and both autosomal dominant and recessive forms have been described. Syndromes in which the hair shaft abnormalities of pili torti are seen in association with other cutaneous and systemic abnormalities include Menkes kinky hair syndrome, Björnstad syndrome (pili torti with deafness; BCS1L gene), and multiple ectodermal dysplasia syndromes.
Menkes Kinky Hair Syndrome (Trichopoliodystrophy)
Males with Menkes kinky hair syndrome, an X-linked recessive trait, are born to an unaffected mother after a normal pregnancy. Neonatal problems include hypothermia, hypotonia, poor feeding, seizures, and failure to thrive. Hair is normal at birth but is replaced by short, fine, brittle, light-colored hair that may have features of trichorrhexis nodosa, pili torti, or monilethrix. The skin is hypopigmented and thin, cheeks typically appear plump, and the nasal bridge is depressed. Progressive psychomotor retardation is noted in early infancy. Mutations in the ATP7A gene, encoding a copper-transporting adenosine triphosphatase protein, cause Menkes kinky hair syndrome. It is a result of maldistribution of the copper in the body. Copper uptake across the brush-border of the small intestine is increased, but copper transport from these cells into the plasma is defective, resulting in low total body copper stores. Parenteral administration of copper-histidine is helpful if begun in the 1st 2 mo of life.

Monilethrix
The hair shaft defect known as monilethrix is inherited as an autosomal dominant trait with variable age of onset, severity, and course. Mutations in the hair keratins HB1, HB3, and HB6 have been identified in autosomal dominant cases, and mutations in desmoglein 4 are found in autosomal recessive cases. The hair appears dry, lusterless, and brittle, and it fractures spontaneously or with mild trauma. Eyebrows, lashes, body and pubic hair, and scalp hair may be affected. Monilethrix is transmitted as an autosomal dominant trait with variable age of onset, severity, and course. Eyebrows and eyelashes are normal. A variant of normal blond hair; an optical effect caused by the refractile quality of the hair shaft that appeared bright in reflected light instead appears dark in the transmitted light as a result of focal aggregates of abnormal air-filled cavities within the shaft. The hair is not fragile. The defect may be autosomal dominant or sporadic in inheritance. Pseudopili annulati is a variant of normal blond hair; an optical effect caused by the refraction and reflection of light from the partially twisted and flattened shaft creates the impression of banding.

Trichorrhexis Invaginata (Bamboo Hair)
Short, sparse, fragile hair without apparent growth is characteristic of trichorrhexis invaginata, which is found primarily in association with Netherton syndrome (see Chapter 658). It has also been reported in other ichthyosiform dermatoses. The distal portion of the hair is invaginated into the cup-like proximal portion, forming a fragile nodal swelling (see Fig. 662-8C).

Pili Annulati
Alternate light and dark bands of the hair shaft characterize pili annulati. When viewed under the light microscope, the region of the hair shaft that appeared bright in reflected light instead appears dark in the transmitted light as a result of focal aggregates of abnormal air-filled cavities within the shaft. The hair is not fragile. The defect may be autosomal dominant or sporadic in inheritance. Pseudopili annulati is a variant of normal blond hair; an optical effect caused by the refraction and reflection of light from the partially twisted and flattened shaft creates the impression of banding.

Woolly Hair Disease
Woolly hair diseases manifest at birth as peculiarly tight, curly, abnormal hair in a non-black person. Autosomal dominant and recessive (PKRY5 gene) types have been described. Woolly hair nevus, a sporadic form, involves only a circumscribed portion of the scalp hair. The affected hair is fine, tightly curled, and light colored, and it grows poorly. Microscopically, an affected hair is oval and shows twisting of 180 degrees on its axis.

Uncombable Hair Syndrome (Spun-Glass Hair)
The hair of patients with uncombable hair syndrome appears disorderly, is often silvery blond (Fig. 662-9), and may break because of repeated, futile efforts to control it. The condition is probably autosomal dominant in inheritance. Eyebrows and eyelashes are normal. A longitudinal depression along the hair shaft is a constant feature, and most hair follicles and shafts are triangular (pili trianguli et canaliculi). The shape of the hair varies along its length, however, preventing the hairs from lying flat.

Bibliography is available at Expert Consult.
Bibliography


Figure 662-9 Disorderly, silvery blond hair in uncombable hair syndrome.
Nail abnormalities in children may be manifestations of generalized skin disease, skin disease localized to the periungual region, systemic disease, drugs, trauma, or localized bacterial and fungal infections (Table 663-1). Nail anomalies are also common in certain congenital disorders (Table 663-2).

ABNORMALITIES IN NAIL SHAPE OR SIZE

Anonychia is absence of the nail plate, usually a result of a congenital disorder or trauma. It may be an isolated finding or may be associated with malformations of the digits. Koilonychia is flattening and concavity of the nail plate with loss of normal contour, producing a spoon-shaped nail (Fig. 663-1). Koilonychia occurs as an autosomal dominant trait or in association with iron-deficiency anemia, Plummer-Vinson syndrome, or hemochromatosis. The nail plate is relatively thin for the 1st yr or 2 of life and, consequently, may be spoon-shaped in otherwise normal children.

Congenital nail dysplasia, an autosomal dominant disorder, manifests at birth as longitudinal streaks and thinning of the nail plate. There is platyonychia and koilonychia, which may overgrow the lateral folds and involve all nails of the toes and fingers.

Nail–patella syndrome is an autosomal dominant disorder in which the nails are 30-50% of their normal size and often have triangular or pyramidal lunulae. The thumbnails are always involved, although in some cases only the ulnar half of the nail may be affected or may be missing. The nails from the index finger to the little finger are progressively less damaged. The patella is also smaller than usual, and this anomaly may lead to knee instability. Bony spines arising from the posterior aspect of the iliac bones, overextension of joints, skin laxity, and renal anomalies may also be present. Nail–patella syndrome is caused by mutations in the transcription factor LMX1B gene.

For a discussion of pachyonychia congenita, see Chapter 658.

Habit tic deformity consists of a depression down the center of the nail with numerous horizontal ridges extending across the nail from it. One or both thumbs are usually involved as a result of chronic rubbing and picking at the nail with an adjacent finger.

Table 663-1

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CLINICAL APPEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Diffuse white</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Mees lines: transverse white lines</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Terry nails: most of nail, zone of pink at distal end</td>
</tr>
<tr>
<td>Congenital leukonychia (autosomal dominant; variety of patterns)</td>
<td>Syndrome of leukonychia, knuckle pads, deafness; isolated finding; partial white</td>
</tr>
<tr>
<td>Darier disease</td>
<td>Longitudinal white streaks</td>
</tr>
<tr>
<td>Half-and-half nail</td>
<td>Proximal white, distal pink azotemia</td>
</tr>
<tr>
<td>High fevers (some diseases)</td>
<td>Transverse white lines</td>
</tr>
<tr>
<td>Hypoalbinemia</td>
<td>Muehrcke lines: stationary paired transverse bands</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Variable white</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Diffuse white</td>
</tr>
<tr>
<td>Pellagra</td>
<td>Diffuse milky white</td>
</tr>
<tr>
<td>Punctate leukonychia</td>
<td>Common white spots</td>
</tr>
<tr>
<td>Tinea and yeast</td>
<td>Variable patterns</td>
</tr>
<tr>
<td>Thallium toxicity (rat poison)</td>
<td>Variable white</td>
</tr>
<tr>
<td>Trauma</td>
<td>Repeated manicure: transverse striations</td>
</tr>
<tr>
<td>Zinc deficiency</td>
<td>Diffuse white</td>
</tr>
</tbody>
</table>

Table 663-2

| Large nails                                  | Pachyonychia congenita, Rubinstein-Taybi syndrome, hemihyppertrophy |
| Smallness or absence of nails                | Ectodermal dysplasias, nail-patella, dyskeratosis congenita, focal dermal hypoplasia, cartilage-hair hypoplasia, Ellis–van Creveld, Larsen, epidermolysis bullosa, incontinentia pigmenti, Rothmund-Thomson, Turner, popliteal web, trisomy 13, trisomy 18, Apert, Gorlin-Pindborg, long arm 21 deletion, otopalatodigital, fetal alcohol, fetal hydantoin, elfin facies, anonychia, acrodermatitis enteropathica |
| Other                                        | Congenital malalignment of the great toenails, familial dystrophic shedding of the nails |

Clubbing of the nails (hippocratic nails) is characterized by swelling of each distal digit, an increase in the angle between the nail plate and the proximal nail fold (Lovibond angle) >180 degrees, and a spongy feeling when one pushes down and away from the interphalangeal joint, because of an increase in fibrovascular tissue between the matrix and the phalanx (Fig. 663-2). The pathogenesis is not known. Nail clubbing is seen in association with diseases of numerous organ systems, including pulmonary, cardiovascular (cyanotic heart disease), gastrointestinal (celiac disease, inflammatory bowel disease), and hepatic (chronic hepatitis) systems, as well as in healthy individuals as an idiopathic or familial finding.

CHANGES IN NAIL COLOR

Leukonychia is a white opacity of the nail plate that may involve the entire plate or may be punctate or striate (see Table 663-1). The nail
Part XXXI  ◆  The Skin

The skin and is of no consequence. Extension or alteration in the pigment should be evaluated by biopsy because of the possibility of malignant change.

Bluish black to greenish nails may be caused by Pseudomonas infection (Fig. 663-4), particularly in association with onycholysis or chronic paronychia. The coloration is caused by subungual debris and pyocyanin pigment from the bacterial organisms.

Yellow nail syndrome manifests as thickened, excessively curved, slow-growing yellow nails without lunulae. All nails are affected in most cases. Associated systemic diseases include bronchiectasis, recurrent bronchitis, chylothorax, and focal edema of the limbs and face. Deficient lymphatic drainage, caused by hypoplastic lymphatic vessels, is believed to lead to the manifestations of this syndrome.

Splinter hemorrhages most often result from minor trauma but may also be associated with subacute bacterial endocarditis, vasculitis, Langerhans cell histiocytosis, severe rheumatoid arthritis, peptic ulcer disease, hypertension, chronic glomerulonephritis, cirrhosis, scurvy, trichinosis, malignant neoplasms, and psoriasis.

Nail Separation

Onycholysis indicates separation of the nail plate from the distal nail bed. Common causes are trauma, long-term exposure to moisture, hyperhidrosis, cosmetics, psoriasis, fungal infection (distal onycholysis), atopic or contact dermatitis, porphyria, drugs (bleomycin, vincristine, retinoid agents, indomethacin, chlorpromazine [Thorazine]), and drug-induced phototoxicity from tetracyclines (Fig. 663-5) or chloramphenicol.

Beau lines are transverse grooves in the nail plate (Fig. 663-6) that represent a temporary disruption of formation of the nail plate. The
leukonychia may also occur. Transverse rows of fine pits are characteristic of alopecia areata. In severe cases, the entire nail surface may be rough. Patients with acrodermatitis enteropathica may have transverse grooves (Beau lines) and nail dystrophy as a result of periungual dermatitis.

**TRACHYONYCHIA (20-NAIL DYSTROPHY)**

Trachyonychia is characterized by longitudinal ridging, pitting, fragility, thinning, distal notching, and opalescent discoloration of all the nails (Fig. 663-8). Patients have no associated skin or systemic diseases and no other ectodermal defects. Its occasional association with alopecia areata has led some authorities to suggest that trachyonychia may reflect an abnormal immunologic response to the nail matrix, whereas histopathologic studies have suggested that it may be a manifestation of lichen planus, psoriasis, or spongiotic (eczematous) inflammation of the nail matrix. The disorder must be differentiated from fungal infections, psoriasis, nail changes of alopecia areata, and nail dystrophy secondary to eczema. Eczema and fungal infections rarely produce changes in all the nails simultaneously. The disorder is self-limited and eventually remits by adulthood.

**NAIL INFECTION**

Fungal infection (onychomycosis) of the nails has been classified into 4 types. White superficial onychomycosis manifests as diffuse or speckled white discoloration of the surface of the toenails. It is caused primarily by *Trichophyton mentagrophytes*, which invades the nail plate. The organism may be scraped off the nail plate with a blade, but treatment is best accomplished by the addition of a topical azole antifungal agent. Distal subungual onychomycosis involves foci of onycholysis under the distal nail plate or along the lateral nail groove, followed by development of hyperkeratosis and yellow-brown discoloration. The process extends proximally, resulting in nail plate thickening.
crumbling (Fig. 663-9), and separation from the nail bed. *Trichophyton rubrum* and, occasionally, *T. mentagrophytes* infect the toenails; finger-nail disease is almost exclusively caused by *T. rubrum*, which may be associated with superficial scaling of the plantar surface of the feet and often of one hand. The dermatophytes are found most readily at the most proximal area of the nail bed or adjacent ventral portion of the involved nail plates. **Topical therapies** such as ciclopirox 8% lacquer or amorolfine 5% lacquer, may be effective for solitary nail infection. Topical efinaconazole 10% may also be effective; laser treatment is an expensive but safe alternative to oral therapy. Because of its long half-life in the nail, oral itraconazole may be effective when given as pulse therapy (1 wk of each month for 3-4 mo). Dosage is weight dependent. Oral daily terbinafine is also quite effective. Either agent is superior to griseofulvin, fluconazole, or ketoconazole. The risks, the most concerning of which is hepatic toxicity, and costs of oral therapy are minimized with the use of pulsed dosing.

**Proximal white subungual onychomycosis** occurs when the organism, generally *T. rubrum*, enters the nail through the proximal nail fold, producing yellow-white portions of the undersurface of the nail plate. The surface of the nail is unaffected. This occurs almost exclusively in immunocompromised patients and is a well-recognized manifestation of AIDS. Treatment includes oral terbinafine or itraconazole.

*Candidal onychomycosis* involves the entire nail plate in patients with chronic mucocutaneous candidiasis. It is also commonly seen in patients with AIDS. The organism, generally *Candida albicans*, enters distally or along the lateral nail folds, rapidly involves the entire thickness of the nail plate, and produces thickening, crumbling, and deformity of the plate. Topical azole antifungal agents may be sufficient for treatment of candidal onychomycosis in an immunocompetent host, but oral antifungal agents are necessary for treatment of patients with immune deficiencies. **Table 663-3** outlines the differential diagnosis of onychomycosis.

### PARONYCHIAL INFLAMMATION

Paronychial inflammation may be acute or chronic and generally involves 1 or 2 nail folds on the fingers. **Acute paronychia** manifests as erythema, warmth, edema, and tenderness of the proximal nail fold, most commonly as a result of pathogenic staphylococci, streptococci, or candidal (Fig. 663-10). Warm soaks and oral agents are generally effective; incision and drainage may be occasionally necessary. Development of chronic paronychia follows prolonged immersion in water (Fig. 663-11), such as occurs in finger or thumb sucking, exposure to irritating solutions, nail fold trauma, or diseases, including Raynaud phenomenon, collagen vascular diseases, and diabetes. Swelling of the proximal nail fold is followed by separation of the nail fold from the underlying nail plate and suppuration. Foreign material, embedded in the dermis of the nail fold, becomes a nidus for inflammation and infection with *Candida* species and mixed bacterial flora. A combination of attention to predisposing factors, meticulous drying of the hands, and long-term topical antifungal agents and topical potent corticosteroids may be required for successful treatment of chronic paronychia.

**Ingrown nail** occurs when the lateral edge of the nail, including spicules that have separated from the nail plate, penetrates the soft

### Table 663-3 | Differential Diagnosis of Onychomycosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>As in onychomycosis: onycholysis, subungual hyperkeratosis, splinter hemorrhages, leuconychia, dystrophy</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Pitting</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Oil drop sign (a translucent yellow-red discoloration seen in the nail bed)</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>Other cutaneous features of psoriasis, family history of psoriasis</td>
</tr>
<tr>
<td>Eczema</td>
<td>Lamellar onychoschizia (lamellar splitting)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>History of repeated soaking in water</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Usually distal portion of nail</td>
</tr>
<tr>
<td>Periungual squamous cell carcinoma/Bowens disease</td>
<td>Periungual squamous cell carcinoma/Bowens disease</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>Single nail, warty changes of nail fold, ooze from edge of nail</td>
</tr>
<tr>
<td>Nails may be shed, painful</td>
<td>Black discoloration of nail plate or nail bed</td>
</tr>
<tr>
<td>Associations with bronchiectasis, lymphoedema, and chronic sinusitis</td>
<td>Pigment can extend onto nail fold</td>
</tr>
<tr>
<td>Lamellar onychoschizia (lamellar splitting)</td>
<td>Pigment can extend onto nail fold</td>
</tr>
<tr>
<td>Nail plate can appear abnormal</td>
<td>Can get associated bleeding</td>
</tr>
<tr>
<td>Nail bed should be normal</td>
<td>Myxoid (mucous) cyst</td>
</tr>
<tr>
<td>Distal onycholysis with repeated trauma</td>
<td>Cyst at base of nail, groove in nail extending length of nail</td>
</tr>
<tr>
<td>Single nail affected, shape of nail changed, homogenous alteration of nail color</td>
<td>Alopecia areata</td>
</tr>
<tr>
<td>Nails are hard with elevated longitudinal curvature</td>
<td>Pits, longitudinal ridging, brittleness</td>
</tr>
<tr>
<td>Nails may be shed, painful</td>
<td>Hair loss</td>
</tr>
</tbody>
</table>

tissue of the lateral nail fold. Erythema, edema, and pain, most often involving the lateral great toes, are noted acutely; recurrent episodes may lead to formation of granulation tissue. Predisposing factors include (1) congenital malalignment (especially of the great toes); (2) compression of the side of the toe from poorly fitting shoes, particularly if the great toes are abnormally long and the lateral nail folds are prominent; and (3) improper cutting of the nail in a curvilinear manner rather than straight across. **Management** includes proper fitting of shoes; allowing the nail to grow out beyond the free edge before cutting it straight across; warm water soaks; oral antibiotics if cellulitis affects the lateral nail fold; and, in severe, recurrent cases, application of silver nitrate to granulation tissue, nail avulsion, or excision of the lateral aspect of the nail followed by matricectomy.

**PARONYCHIAL TUMORS**

Tumors in the paronychial area include pyogenic granulomas, mucous cysts, subungual exostoses, and junctional nevi. Periungual fibromas that appear in late childhood should suggest a diagnosis of tuberous sclerosis.

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


The mucous membranes may be involved in developmental disorders, genodermatoses, infections, acute and chronic skin diseases, or benign and malignant tumors.

**ANGULAR CHEILITIS**
Angular cheilitis (perlèche) is characterized by inflammation and fissuring at the corners of the mouth, often with associated erosion, maceration, and crusting (Fig. 664-1). Chapping or moisture collection at the angles of the mouth predispose children to developing angular cheilitis. Children who are chronic lip lickers or who have excessive salivation or drooling related to neurologic deficits, orthodontic appliances, or mouth breathing are at increased risk. Atopic dermatitis or contact dermatitis related to toothpaste, chewing gum, mouthwash, or cosmetics are also common causes. Nutritional deficiencies are a less-frequent etiology. Protection can be provided by frequent application of a bland ointment such as petrolatum. Candidosis should be treated with an appropriate antifungal agent, and contact dermatitis of the perioral skin should be treated with a low-potency topical corticosteroid ointment preparation and frequent use of petrolatum or a similar emollient. Correction of the underlying predisposing factors (if possible) will prevent recurrence.

**APHTHOUS STOMATITIS (CANKER SORES)**
Aphthous stomatitis consists of solitary or multiple painful ulcerations occur on the labial (Fig. 664-2), buccal, lingual, sublingual, palatal, or gingival mucosa (see Chapter 315). Lesions may manifest initially as erythematous, indurated papules that erode rapidly to form sharply circumscribed, necrotic ulcers with a gray fibrinous exudate and an erythematous halo. Minor aphthous ulcers are 2-10 mm in diameter and heal spontaneously in 7-10 days. Major aphthous ulcers are >10 mm in diameter, take from 10-30 days to heal, and may heal with scarring. A third type of aphthous ulceration is herpetiform in appearance, manifesting as a few to numerous grouped 1-2 mm lesions which tend to coalesce into plaques and heal over 7-10 days. Approximately 30% of patients with recurrent lesions have a family history of the disorder (see Chapter 315 for the differential diagnosis).

The etiology of aphthous stomatitis is multifactorial; the condition probably represents an oral manifestation of a number of conditions. Altered local regulation of the cell-mediated immune system, after activation and accumulation of cytotoxic T cells, may contribute to the
localized mucosal breakdown. It is a common misconception that aphthous stomatitis is a manifestation of herpes simplex virus infection. Recurrent herpes infections remain localized to the lips and rarely cross the mucocutaneous junction; involvement of the oral mucosa occurs only in primary infections.

Treatment of aphthous stomatitis is palliative. The majority of mild cases do not require therapy. Relief of pain, particularly before eating, may be achieved with the use of a topical anesthetic such as viscous lidocaine or an oral rinse with a combined solution of elixir of diphenhydramine, viscous lidocaine, and an oral antacid. Caution must be taken to avoid hot food and drink after topical anesthetic use. A superpotent topical corticosteroid in a mucosa-adhering agent may help reduce inflammation, and topical tetracycline mouthwash may also hasten healing. In severe, debilitating cases, systemic therapy with corticosteroids, colchicine, dapsone, or thalidomide may be helpful.

**FISSURED TONGUE**

Fissured tongue (scrotal tongue, or lingua plicata) is a common benign developmental anomaly of the tongue. The dorsal tongue has many folds with deep grooves and a pebbled appearance. Fissured tongue can be seen in individuals with Melkersson-Rosenthal syndrome and Down syndrome, and it is often seen in association with geographic tongue. Food particles and debris may become trapped in the fissures, resulting in irritation, inflammation, and halitosis. Careful cleansing with a mouth rinse and soft-bristled toothbrush is recommended.

**GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS)**

Geographic tongue consists of single or multiple sharply demarcated, irregular, smooth red patches surrounded by an elevated whitish-red serpiginous border on the dorsum of the tongue. Onset is rapid, and the pattern may change over hours to days. The smooth patches correspond to atrophic filiform papillae, and the elevated margins represent hypertrophic papillae (Fig. 664-4). The etiology of this condition remains unclear. Lesions are typically asymptomatic, but some patients may experience a burning sensation or sensitivity to spicy, hot, or cold foods. No therapy other than reassurance is necessary.

**BLACK HAIRY TONGUE**

Black hairy tongue is a dark coating on the dorsum of the tongue caused by hyperplasia and elongation of the filiform papillae; overgrowth of chromogenic bacteria and fungi and entrapped pigmented residues that adsorb to microbial plaque and desquamating keratin may contribute to the dark coloration. Changes often begin posteriorly and extend anteriorly on the dorsum of the tongue. The condition is most common in adults but may also manifest during adolescence. Poor oral hygiene, lack of oral feeding, treatment with systemic antibiotics such as tetracycline (which promote the growth of Candida spp.), and smoking are predisposing factors. Improved oral hygiene and brushing with a soft-bristled toothbrush may be all that is necessary for treatment.

**MUCOCELE**

Mucous retention cysts are painless, fluctuant, tense, 2-10 mm, bluish papules on the lips (Fig. 664-3), tongue, palate, or buccal mucosa. Traumatic severance of the duct of a minor salivary gland leads to submucosal retention of mucus secretion. Lesions on the floor of the mouth are known as ranulas when the sublingual or submandibular salivary gland ducts are involved. Fluctuations in size are typical, and the lesions may disappear temporarily after traumatic rupture. Recurrence is prevented by surgical excision of the mucus deposit and associated salivary gland(s).

**FORDYCE SPOTS**

Fordyce spots (Fordyce granules) are asymptomatic, 1-3 mm, yellow-white macules and papules on the vermilion lips and buccal mucosa. They are a common clinical finding and represent a normal anatomic variant of sebaceous glands. They can present in either sex from infancy to adulthood and may become more prominent during puberty due to the influence of androgens. No therapy is required.

**EPSTEIN PEARLS (GINGIVAL CYSTS OF THE NEWBORN)**

Epstein pearls are white, keratin-containing cysts on the palatal or alveolar mucosa of approximately 80% of neonates. They are epidermal inclusion cysts that form when the soft and hard palates fuse and are analogous to facial milia. They cause no symptoms and are generally shed within a few weeks; no therapy is necessary.

**ACUTE NECROTIZING ULCERATIVE GINGIVITIS (VINCENT STOMATITIS, FUSOSPIROCHETAL GINGIVITIS, TRENCH MOUTH)**

Acute necrotizing ulcerative gingivitis manifests as painful punched-out ulceration, necrosis, and bleeding of the interdental papillae. A
grayish-white pseudomembrane may cover the ulcerations. Lesions may spread to involve the buccal mucosa, lips, tongue, tonsils, and pharynx and may be associated with dental pain, a bad taste, low-grade fever, and lymphadenopathy. It occurs most commonly in the 2nd or 3rd decade, particularly in the context of poor dental hygiene, poor nutrition, smoking, and stress.

NOMA
Noma is a severe form of fusospirillary gangrenous stomatitis that occurs primarily in malnourished, impoverished children 2-5 yr of age who have had a preceding illness such as measles, scarlet fever, tuberculosis, malignancy, or immunodeficiency. The disease is most prevalent in Africa, but also occurs in Asia and Latin America. Sporadic cases associated with immunodeficiency have been reported in developed countries. It manifests as a painful, red, indurated papule on the alveolar margin, followed by ulceration and mutilating gangrenous destruction of tissue in the oronasal region. The process may also involve the scalp, neck, shoulders, perineum, and vulva. Noma neonatorum manifests in the 1st mo of life as gangrenous lesions of the lips, nose, mouth, and anal regions. Affected infants are usually small for gestational age, malnourished, premature, and frequently ill (particularly with *Pseudomonas aeruginosa* sepsis). Care consists of nutritional support, conservative debridement of necrotic soft tissues, empirical broad-spectrum antibiotics such as penicillin and metronidazole, and, in the case of noma neonatorum, antipseudomonal antibiotics (see Chapter 46).

COWDEN SYNDROME (MULTIPLE HAMARTOMA SYNDROME)

Cowden syndrome is an autosomal dominant condition caused by loss-of-function mutations in the *PTEN* tumor-suppressor gene. Mucocutaneous lesions typically appear in the 2nd or 3rd decade. Oral papillomas are 1-3 mm smooth, pink or whitish papules on the palatal, gingival, buccal, and labial mucosae and may coalesce into a cobblestone appearance. Numerous flesh-colored papules also develop on the face, particularly around the mouth, nose, and ears. These papules are most commonly trichilemmomas, a benign neoplasm of the hair follicle. Associated findings may include acral keratoses, thyroid adenoma, goiter, gastrointestinal polyps, fibrocystic breast nodules, and carcinoma of the breast or thyroid.

*Bibliography is available at Expert Consult.*
Bibliography
Chapter 665  •  Cutaneous Bacterial Infections

665.1 Impetigo

Anna M. Juern and Beth A. Drolet

ETIOLOGY/PATHOGENESIS

Impetigo is the most common skin infection in children throughout the world. There are 2 classic forms of impetigo: nonbullous and bullous.

Staphylococcus aureus is the predominant organism of nonbullous impetigo in the United States; group A β-hemolytic streptococci (GABHS) are implicated in the development of some lesions. The staphylococcal types that cause nonbullous impetigo are variable but are not generally from phage group 2, the group that is associated with scalded skin and toxic shock syndromes. Staphylococci generally spread from the nose to normal skin and then infect the skin. In contrast, the skin becomes colonized with GABHS an average of 10 days before development of impetigo. The skin serves as the source for acquisition of GABHS and the probable primary source for spread of impetigo. Lesions of nonbullous impetigo that grow staphylococci in culture cannot be distinguished clinically from those that grow pure cultures of GABHS.

Bullous impetigo is always caused by S. aureus strains that produce exfoliative toxins. The staphylococcal exfoliative toxins (ETA, ETB, ETD) blister the superficial epidermis by hydrolyzing human desmoglein 1, resulting in a subcorneal vesicle. This is also the target antigen of the autoantibodies in pemphigus foliaceus (see Chapters 181 and 183).

CLINICAL MANIFESTATIONS

Nonbullous Impetigo

Nonbullous impetigo accounts for more than 70% of cases. Lesions typically begin on the skin of the face or on extremities that have been traumatized. The most common lesions that precede nonbullous impetigo are insect bites, abrasions, lacerations, chickenpox, scabies pediculosis, and burns. A tiny vesicle or pustule forms initially and rapidly develops into a honey-colored crusted plaque that is generally <2 cm in diameter (Fig. 665-1). The infection may be spread to other parts of the body by the fingers, clothing, and towels. Lesions are associated with little to no pain or surrounding erythema, and constitutional symptoms are generally absent. Pruritus occurs occasionally, regional adenopathy is found in up to 90% of cases, and leukocytosis is present in approximately 50%.

Bullous Impetigo

Bullous impetigo is mainly an infection of infants and young children. Flaccid, transparent bullae develop most commonly on skin of the face, buttocks, trunk, perineum, and extremities. Neonatal bullous impetigo can begin in the diaper area. Rupture of a bulla occurs easily, leaving a narrow rim of scale at the edge of shallow, moist erosion. Surrounding erythema and regional adenopathy are generally absent. Unlike those of nonbullous impetigo, lesions of bullous impetigo are a manifestation of localized staphylococcal scalded skin syndrome and develop on intact skin.

Differential Diagnosis

The differential diagnosis of nonbullous impetigo includes viruses (herpes simplex, varicella-zoster), fungi (tinea corporis, kerion),...
arrthropod bites, and parasitic infestations (scabies, pediculosis capitis), all of which may become impetiginized.

The differential diagnosis of bullous impetigo in neonates includes epidermolysis bullosa, bullous mastocytosis, herpetic infection, and early scalded skin syndrome. In older children, allergic contact dermatitis, burns, erythema multiforme, linear immunoglobulin A dermatosis, pemphigus, and bullous pemphigoid must be considered, particularly if the lesions do not respond to therapy.

**COMPLICATIONS**

Potential but very rare complications of either nonbullous or bullous impetigo include osteomyelitis, septic arthritis, pneumonia, and septicemia. Positive blood culture results are very rare in otherwise healthy children with localized lesions. Cellulitis has been reported in up to 10% of patients with nonbullous impetigo and rarely follows the bullous form. Lymphangitis, supplicative lymphadenitis, gultate psoirasis, and scarlet fever occasionally follow streptococcal disease. There is no correlation between number of lesions and clinical involvement of the lymphatics or development of cellulitis in association with streptococcal impetigo.

Infection with nephritogenic strains of GABHS may result in acute poststreptococcal glomerulonephritis (see Chapter 511.1). The clinical character of impetigo lesions is not predictive of the development of poststreptococcal glomerulonephritis. The most commonly affected age group is children 3-7 yr of age. The latent period from onset of impetigo to development of poststreptococcal glomerulonephritis averages 18-21 days, which is longer than the 10-day latency period after pharyngitis. Poststreptococcal glomerulonephritis occurs epidemically after either pharyngeal or skin infection. Impetigo-associated epidemics have been caused by M groups 2, 49, 53, 56, 57, and 60. Strains of GABHS that are associated with endemic impetigo in the United States have little or no nephritogenic potential. Acute rheumatic fever does not occur as a result of impetigo.

**TREATMENT**

The decision on how to treat impetigo depends on the number of lesions and their locations. Topical therapy with mupirocin 2%, and retapamulin 1% 2-3 times a day for 10-14 days is acceptable for localized disease caused by *S. aureus*.

Systemic therapy with oral antibiotics should be prescribed for patients with streptococcal or widespread involvement of staphylococcal infections; when lesions are near the mouth, where topical medication may be licked off; or in cases with evidence of deep involvement, including cellulitis, furunculosis, abscess formation, or supplicative lymphadenitis. Cephalexin, 25-50 mg/kg/day in 3-4 divided doses for 7-10 days, is an excellent choice for initial therapy. No evidence suggests that a 10-day course of therapy is superior to a 7-day course. The emergence of methicillin-resistant *S. aureus* (MRSA) dictates that if a satisfactory clinical response is not achieved within 7 days, a culture should be performed and an appropriate antibiotic based on drug sensitivity should be given for an additional 7 days. If MRSA is suspected, clindamycin, doxycycline or sulfamethoxazole-trimethoprim is indicated.

**Bibliography**

Bibliography is available at Expert Consult.

### 665.2 Subcutaneous Tissue Infections

Anna M. Juern and Beth A. Drolet

The principal determinations for soft-tissue infections is whether it is *nonnecrotizing* or *necrotizing*, as well as *purulent* or *nonpurulent* (see Fig. 665-1). The former responds to antibiotic therapy alone, whereas the latter requires prompt surgical removal of all devitalized tissue in addition to antimicrobial therapy. Necrotizing soft-tissue infections are life-threatening conditions that are characterized by rapidly advancing local tissue destruction and systemic toxicity. Tissue necrosis distinguishes them from cellulitis. In cellulitis, an inflammatory infectious process involves subcutaneous tissue but does not destroy it. Necrotizing soft-tissue infections characteristically manifest with a paucity of early cutaneous signs relative to the rapidity and degree of destruction of the subcutaneous tissues.

**CELLULITIS**

**Etiology**

Cellulitis is characterized by infection and inflammation of loose connective tissue, with limited involvement of the dermis and relative sparing of the epidermis. A break in the skin from previous trauma, surgery, or an underlying skin lesion predisposes to cellulitis. Cellulitis is also more common in individuals with lymphatic stasis, diabetes mellitus, or immunosuppression.

*a Streptococcus pyogenes* (group A streptococcus) and *S. aureus* are the most common etiologic agents. In patients who are immunocompromised or have diabetes mellitus, a number of other bacterial or fungal agents may be involved, notably *Pseudomonas aeruginosa; Aeromonas hydrophila* and, occasionally, other Enterobacteriaceae; *Legionella* spp.; the Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp.; and *Cryptococcus neoformans*. Children with relapsed nephrotic syndrome may experience cellulitis caused by *Escherichia coli*. In children age 3 mo to 5 yr, *Haemophilus influenzae* type b was once an important cause of facial cellulitis, but its incidence has declined significantly since the institution of immunization against this organism.

**Clinical Manifestations**

Cellulitis manifests clinically as an area of edema, warmth, erythema, and tenderness. The lateral margins tend to be indistinct because the process is deep in the skin, primarily involving the subcutaneous tissues in addition to the dermis. Application of pressure may produce pitting. Although distinction cannot be made with certainty in any particular patient, cellulitis due to *S. aureus* tends to be more localized and may suppurate, whereas infections caused by *S. pyogenes* (group A streptococci) tend to spread more rapidly and may be associated with lymphangitis. Regional adenopathy and constitutional signs and symptoms such as fever, chills, and malaise are common. Complications of cellulitis are uncommon but include subcutaneous abscess, bacteremia, osteomyelitis, septic arthritis, thrombophlebitis, endocarditis, and necrotizing fasciitis. Lymphangitis or glomerulonephritis can also follow infection with *S. pyogenes*.

**Diagnosis**

Aspirates from the site of inflammation, skin biopsy, and blood cultures allow identification of the causal organism in approximately 25% of cases of cellulitis. Blood cultures are usually negative in immunocompetent patients with mild to moderate infection. Yield of the causative organism is approximately 30% when the site of origin of the cellulitis is apparent, such as an abrasion or ulcer. An aspirate taken from the point of maximum inflammation yields the causal organism more often than a leading-edge aspirate. Lack of success in isolating an organism stems primarily from the low number of organisms present within the lesion. Ultrasonography is used if an associated subcutaneous abscess is suspected.

The differential diagnosis should include an exuberant immune-allergic reaction to insect bites particularly mosquito bites (Skeeter syndromes) (see Chapter 146). The skeeter syndrome is characterized by swelling disproportionate to erythema; there is pruritus but usually no tenderness. In addition, cold panniculitis may appear as an erythematous but usually nontender swelling after exposure to cold, such as sledding or eating a cold Popsicle (see Chapter 660.1).

**Treatment**

Empirical therapy for cellulitis should be directed by the history of the illness, the location and severity of the cellulitis, and the age and immune status of the patient (Fig. 665-2). Cellulitis in a neonate should prompt a full sepsis evaluation, followed by initiation of empirical intravenous therapy with a β-lactamase–stable antistaphylococcal antibiotic such as mexiticillin or vancomycin and an aminoglycoside such as gentamicin or a cephalosporin such as cefotaxime. Treatment of
Bibliography


cellulitis in an infant or child younger than about 5 yr of age should provide coverage for *S. pyogenes* and *S. aureus* as well as *H. influenzae* type b and *Streptococcus pneumoniae*. The evaluation should include a blood culture, and if the infant is younger than 1 yr of age, if signs of systemic toxicity are present, or if an adequate examination cannot be carried out, a lumbar puncture should also be performed. In most cases of cellulitis on an extremity, regardless of age, *S. aureus* and *S. pyogenes* are the cause and bacteremia is highly unlikely in an otherwise well-appearing child. Blood cultures should be performed if sepsis is suspected.

If fever, lymphadenopathy, and other constitutional signs are absent (white blood cell count <15,000), treatment of cellulitis on an extremity may be initiated orally on an outpatient basis with a penicillinase-resistant penicillin such as dicloxacillin or cloxacillin or a first-generation cephalosporin such as cephalexin or, if MRSA is suspected, with clindamycin. If improvement is not noted or the disease progresses significantly in the 1st 24-48 hr of therapy, parenteral therapy is necessary. If fever, lymphadenopathy, or constitutional signs are present, parenteral therapy should be initiated. Oxacillin or nafcillin is effective in most cases, although if systemic toxicity is significant, consideration should be given to the addition of clindamycin or vancomycin. Three new agents for skin and skin structure infections have been approved by the FDA in adults. Dalbavancin (intravenous given once weekly; active against MRSA; *S. pyogenes*, and vancomycin-resistant enterococcus and *S. aureus*), tedizolid (oral or IV given bid, active against MRSA, *S. pyogenes*, coagulase-negative *Staphylococcus*), and oritavancin (IV; active against MRSA, *S. pyogenes*). Once the erythema, warmth, edema, and fever have decreased significantly, a 10-day course of treatment may be completed on an outpatient basis. Immobilization and elevation of an affected limb, particularly early in the course of therapy, may help reduce swelling and pain. If present, a subcutaneous abscess should be drained.

### NECROTIZING FASCIITIS

**Etiology**

Necrotizing fasciitis is a subcutaneous tissue infection that involves the deep layer of superficial fascia but may spare adjacent epidermis, deep fascia, and muscle. Relatively few organisms possess sufficient virulence to cause necrotizing fasciitis when acting alone. The majority (55-75%) of cases of necrotizing fasciitis are polymicrobial in nature (synergistic necrotizing fasciitis), with an average of 4 different organisms isolated. The

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**Figure 665-2 Purulent skin and soft-tissue infections (SSTIs)—Mild infection:** For purulent SSTI, incision and drainage is indicated. **Moderate infection:** Patients with purulent infection with systemic signs of infection. **Severe infection:** Patients who have failed incision and drainage plus oral antibiotics or those with systemic signs of infection such as temperature >38°C (100.4°F), tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >24 breaths/min) or abnormal white blood cell count (<12,000 or <400 cells/µL), or immunocompromised patients. **Nonpurulent SSTIs—Mild infection:** Typical cellulitis/erysipelas with no focus of purulence. **Moderate infection:** Typical cellulitis/erysipelas with systemic signs of infection. **Severe infection:** Patients who have failed oral antibiotic treatment or those with systemic signs of infection (as defined above under purulent infection), or those who are immunocompromised, or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or evidence of organ dysfunction. Three newer agents, oritavancin, tedizolid, and dalbavancin, are also effective agents in SSTIs, including those caused by methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; C&S, culture and sensitivity; I & D, incision and drainage; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; Rx, treatment; TMP/SMX, trimethoprim-sulfamethoxazole. (Modified from Stevens DL, Bisno AL, Chambers HF, et al: Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 59:147–159, 2014, Fig. 1.)
organisms most commonly isolated in polymicrobial necrotizing fasciitis are *S. aureus*, streptococcal species, *Klebsiella* species, *E. coli*, and anaerobic bacteria. The rest of the cases and the most fulminant infections, associated with toxic shock syndrome and a high case fatality rate, are usually caused by *S. pyogenes* (group A streptococcus) (see Chapter 183). Streptococcal necrotizing fasciitis may occur in the absence of toxic shock–like syndrome and is potentially fatal and associated with substantial morbidity. Necrotizing fasciitis can occasionally be caused by *S. aureus*, *Clostridium perfringens*, *Clostridium septicum*, *P. aeruginosa*, *Vibrio spp.*, particularly *Vibrio vulnificus*; and fungi of the order Mucorales, particularly *Rhizopus spp.*, *Mucor spp.*, and *Absidia* spp. Necrotizing fasciitis has also been reported, on rare occasions, to result from non–group A streptococci such as group B, C, F, or G streptococci, *S. pneumoniae*, or *H. influenzae* type b.

Infections caused by any 1 organism or combination of organisms cannot be distinguished clinically from one another, although development of *crepitis* signals the presence of *Clostridium* spp. or Gram-negative bacilli such as *E. coli*, *Klebsiella*, *Proteus*, or *Aeromonas*.

**Clinical Manifestations**

Necrotizing fasciitis may occur anywhere on the body. Polymicrobial infections tend to occur on perineal and trunk areas. The incidence of necrotizing fasciitis is highest in hosts with systemic or local tissue immunocompromise, such as those with diabetes mellitus, neoplasia, or peripheral vascular disease as well as those who have recently undergone surgery, who abuse intravenous drugs, or who are undergoing immunosuppressive treatment, particularly with corticosteroids. The infection can also occur in healthy individuals after minor puncture wounds, abrasions, or lacerations; blunt trauma; surgical procedures, particularly of the abdomen, gastrointestinal or genitourinary tracts, or the perineum; or hypodermic needle injection.

There has been a resurgence of fulminant necrotizing soft-tissue infections caused by *S. pyogenes*, which may occur in previously healthy individuals. Streptococcal necrotizing fasciitis is classically located on an extremity. There may be a history of recent trauma to or operation in the area. Necrotizing fasciitis due to *S. pyogenes* may also occur after superinfection of varicella lesions. Children with this disease have tended to display onset, recrudescence, or persistence of high fever and signs of toxicity after the 3rd or 4th day of varicella. Common predisposing conditions in neonates are omphalitis and biliary atresia, particularly of the abdomen, gastrointestinal or genitourinary tracts, and pain, tenderness, and constitutional signs are disproportionate to the disease in both animal models and human volunteers. Decreased epidermolytic or exfoliative toxins A or B. The toxins have reproduced in cultures of *S. pyogenes* when incubated with normal human skin, and are seen.

**Diagnosis**

Definitive diagnosis of necrotizing fasciitis is made by surgical exploration, which should be undertaken as soon as the diagnosis is suspected. Necrotic fascia and subcutaneous tissue are gray and offer little resistance to blunt probing. Although CT and MRI aids in delineating the extent and tissue planes of involvement, this procedure should not delay surgical intervention. Frozen-section incisional biopsy specimens obtained early in the course of the infection can aid management by decreasing the time to diagnosis and helping establish margins of involvement. Gram staining of tissue can be particularly useful if chains of Gram-positive cocci, indicative of infection with *S. pyogenes*, are seen.

**Treatment**

Early supportive care, surgical debridement, and parenteral antibiotic administration are mandatory for necrotizing fasciitis. All devitalized tissue should be removed to freely bleeding edges, and repeat exploration is generally indicated within 24-36 hr to confirm that no necrotic tissue remains. This procedure may need to be repeated on several occasions until devitalized tissue has ceased to form. Meticulous daily wound care is also paramount.

Parenteral antibiotic therapy should be initiated as soon as possible with broad-spectrum agents against all potential pathogens. Initial empirical therapy should be instituted with vancomycin, linezolid, daptomycin, or quinupristin to cover Gram-positive and piperacillin-tazobactam to cover Gram-negative organisms. An alternative is to add ceftriaxone with metronidazole to cover mixed aerobic–anaerobic organisms. Therapy should then be based on sensitivity of isolated organisms. Penicillin with clindamycin is indicated for documented group A streptococcal necrotizing fasciitis. Some centers employ hyperbaric oxygen therapy, although it should not delay resuscitation or surgical debridement.

**Prognosis**

The combined case fatality rate among children and adults with necrotizing fasciitis and syndrome due to polymicrobial infection or *S. pyogenes* has been as high as 60%. Death is less common in children, however, and in cases not complicated by toxic shock–like syndrome.

**Bibliography**

*Available at Expert Consult.*

### 665.3 Staphylococcal Scalded Skin Syndrome (Ritter Disease)

Anna M. Juern and Beth A. Drolet

**ETIOLOGY AND PATHOGENESIS**

Staphylococcal scalded skin syndrome is caused predominantly by phage group 2 staphylococci, particularly strains 71 and 55, which are present at localized sites of infection. Foci of infection include the nasopharynx and, less commonly, the umbilicus, urinary tract, a superficial abrasion, conjunctivae, and blood. The clinical manifestations of staphylococcal scalded skin syndrome are mediated by hematogenous spread, in the absence of specific antitoxin antibody of staphylococcal epidermolytic or exfoliative toxins A or B. The toxins have reproduced the disease in both animal models and human volunteers. Decreased renal clearance of the toxins may account for the fact that the disease is most common in infants and young children, as well as lack of protection from antitoxin antibodies. Epidermolytic toxin A is heat stable and is encoded by bacterial chromosomal genes. Epidermolytic toxin B is heat labile and is encoded on a 37.5-kb plasmid. The site of blister cleavage is subcorneal. The epidermolytic toxins produce the split by binding to and cleaving desmoglein 1. Intact bullae are consistently may develop, manifesting as tight edema, pain on motion, and loss of distal sensation and pulses; this is a surgical emergency.
Bibliography


sterile, unlike those of bullous impetigo, but culture specimens should be obtained from all suspected sites of localized infection and from the blood to identify the source for elaboration of the epidermolytic toxins.

**CLINICAL MANIFESTATIONS**

Staphylococcal scalded skin syndrome, which occurs predominantly in infants and children younger than 5 yr of age, includes a range of disease from localized bullous impetigo to generalized cutaneous involvement with systemic illness. Onset of the rash may be preceded by malaise, fever, irritability, and exquisite tenderness of the skin. Scarringlatiniform erythema develops diffusely and is accentuated in flexural and periorificial areas. The conjunctivae are inflamed and occasionally become purulent. The brightly erythematous skin may rapidly acquire a wrinkled appearance, and in severe cases, sterile, flaccid blisters and erosions develop diffusely. Circumoral erythema is characteristically prominent, as is radial crusting and fissuring around the eyes, mouth, and nose. At this stage, areas of epidermis may separate in response to gentle shear force (Nikolsky sign; Fig. 665-3). As large sheets of epidermis peel away, moist, glistening, denuded areas become apparent, initially in the flexures and subsequently over much of the body surface (Fig. 665-4). This development may lead to secondary cutaneous infection, sepsis, and fluid and electrolyte disturbances. The desquamative phase begins after 2-5 days of cutaneous erythema; healing occurs without scarring in 10-14 days. Patients may have pharyngitis, conjunctivitis, and superficial erosions of the lips, but intraoral mucosal surfaces are spared. Although some patients appear ill, many are reasonably comfortable except for the marked skin tenderness.

**DIFFERENTIAL DIAGNOSIS**

A presumed abortive form of the disease manifests as diffuse, scarlatiniform, tender erythoderma that is accentuated in the flexural areas but does not progress to blister formation. In patients with this form, Nikolsky sign may be absent. Although the exanthem is similar to that of streptococcal scarlet fever, strawberry tongue and palatal petechiae are absent. Staphylococcal scalded skin syndrome may be mistaken for a number of other blistering and exfoliating disorders, including bullous impetigo, epidermolysis bullosa, epidermolytic hyperkeratosis, pemphigus, drug eruption, erythema multiforme, and drug-induced toxic epidermal necrolysis. Toxic epidermal necrolysis can often be distinguished by a history of drug ingestion, the presence of Nikolsky sign only at sites of erythema, absence of perioral crusting, full-thickness epidermal necrosis, and a blister cleavage plane in the lowermost epidermis.

**HISTOLOGY**

A subcorneal, granular layer split can be identified on skin biopsy. Absence of an inflammatory infiltrate is characteristic. Histology is identical to that seen in pemphigus foliaceus and subcorneal pustular dermatosis.

**TREATMENT**

Systemic therapy, given either orally in cases of localized involvement or parenterally with a semisynthetic penicillinase-resistant penicillin or vancomycin if MRSA is considered, should be prescribed. Clindamycin should be added to inhibit bacterial protein (toxin) synthesis. The skin should be gently moistened and cleansed. Application of an emollient provides lubrication and decreases discomfort. Topical antibiotics are unnecessary. In neonates, or in infants or children with severe infection, hospitalization is mandatory, with attention to fluid and electrolyte management, infection control measures, pain management, and meticulous wound care with contact isolation. In particularly severe disease, care in an intensive care or burn unit is required. Recovery is usually rapid, but complications such as excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, sepsis, and cellulitis may cause increased morbidity.

**Figure 665-3** Nikolsky sign. With slight thumb pressure the skin wrinkles, slides laterally, and separates from the dermis. (From Habif TP, editor: Clinical dermatology, ed 4, Philadelphia, 2004, Mosby.)

**Figure 665-4** Infant with staphylococcal scalded skin syndrome.

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**665.4 Ecthyma**

Anna M. Juern and Beth A. Drolet

See also Chapters 181, 183, 205.

Ecthyma resembles nonbullous impetigo in onset and appearance but gradually evolves into a deeper, more chronic infection. The initial lesion is a vesicle or pustule with an erythematous base that erodes through the epidermis into the dermis to form an ulcer with elevated margins. The ulcer becomes obscured by a dry, heaped-up, tightly adherent crust (Fig. 665-5) that contributes to the persistence of the infection and scar formation. Lesions may be spread by autoinoculation, may be as large as 4 cm, and occur most frequently on the
Bibliography


The skin may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and abscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The differential diagnosis includes deep fungal infection, particularly blastomycosis (Fig. 665-7) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

Blistering distal dactylitis is a superficial blistering infection of the volar fat pad on the distal portion of the finger or thumb (Fig. 665-8). More than 1 finger may be involved, as may the volar surfaces of the proximal phalanges, palms, and toes. Blistering distal dactylitis is caused most commonly by group A streptococcus but has also occurred as a result of infection with S. aureus. If left untreated, blisters may continue to enlarge and may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and abscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The differential diagnosis includes deep fungal infection, particularly blastomycosis (Fig. 665-7) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

Ecthyma gangrenosum is a necrotic ulcer covered with a gray-black eschar. It is usually a sign of P. aeruginosa sepsis and usually occurs in immunosuppressed patients. Neutropenia is a risk factor for ecthyma gangrenosum. Ecthyma gangrenosum occurs in up to 6% of patients with systemic P. aeruginosa infection but can also occur as a primary cutaneous infection by inoculation. The lesion begins as a red or purpuric macule that vesiculates and then ulcerates. There is a surrounding rim of pink to violaceous skin. The punched-out ulcer develops raised edges with a dense, black, depressed, crusted center. Lesions may be single or multiple. Patients with bacteremia commonly have lesions in acropinic areas. Clinically similar lesions may also develop as a result of infection with other agents, such as S. aureus, A. hydrophila, Entero bacter spp., Proteus spp., Burkholderia cepacia, Serratia marcescens, Aspergillus spp., Mucorales, E. coli, and Candida spp. There is bacterial invasion of the adventitia and media of dermal veins but not arteries. The intima and lumina are spared. Blood and skin biopsy specimens for culture should be obtained, and empirical broad-spectrum, systemic therapy that includes coverage for Pseudomonas (i.e., aminoglycoside and an antipseudomonal penicillin) should be initiated as soon as possible.

Bibliography is at Expert Consult.

665.5 Other Cutaneous Bacterial Infections
Anna M. Juern and Beth A. Drolet

BLASTOMYCOSIS-LIKE PYODERMA (PYODERMA VEGETANS)
Blastomycosis-like pyoderma is an exuberant cutaneous reaction to bacterial infection that occurs primarily in children who are malnourished and immunosuppressed. The organisms most commonly isolated from lesions are S. aureus and group A streptococcus, but several other organisms have been associated with these lesions, including P. aeruginosa, Proteus mirabilis, diphtheroids, Bacillus spp., and C. perfringens. Crusted, hyperplastic plaques on the extremities are characteristic, sometimes forming from the coalescence of many pinpoint, purulent, crusted abscesses (Fig. 665-6). Ulceration and sinus tract formation may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and abscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The differential diagnosis includes deep fungal infection, particularly blastomycosis (Fig. 665-7) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

BLISTERING DISTAL DACTYLITIS
Blistering distal dactylitis is a superficial blistering infection of the volar fat pad on the distal portion of the finger or thumb (Fig. 665-8). More than 1 finger may be involved, as may the volar surfaces of the proximal phalanges, palms, and toes. Blistering distal dactylitis is caused most commonly by group A streptococcus but has also occurred as a result of infection with S. aureus. If left untreated, blisters may continue to enlarge and
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and tender to touch. At this stage, a white pseudomembrane may be present. As the rash becomes more chronic, the perianal eruption may consist of painful fissures, a dried mucoid discharge, or psoriasiform plaques with yellow peripheral crust. In girls, the perianal rash may be associated with vulvovaginitis. In boys, the penis may be involved. Approximately 50% of patients have rectal pain, most commonly described as burning inside the anus during defecation, and 33% have blood-streaked stools. Fecal retention is a frequent behavioral response to the infection. Patients also have presented with guttate psoriasis. Although local induration or edema may occur, constitutional symptoms such as fever, headache, and malaise are absent, suggesting that subcutaneous involvement, as in cellulitis, is absent. Familial spread of perianal infectious dermatitis is common, particularly when family members bathe together or use the same water.

Perianal infectious dermatitis is usually caused by GABHS, but it may also be caused by S. aureus. The index case and family members should undergo culture; follow-up cultures to document bacteriologic cure after a course of treatment are recommended.

The differential diagnosis of perianal infectious dermatitis includes psoriasis, seborrheic dermatitis, candidiasis, pinworm infestation, sexual abuse, and inflammatory bowel disease.

For GABHS perianal infectious dermatitis, treatment with a 7-day course of cefuroxime (20 mg/kg/day in 2 divided doses) is superior to treatment with penicillin. Concomitant topical mupirocin ointment 2-3 times a day also may be used. If S. aureus is cultured, treatment should be based on sensitivities.

**ERYSIPelas**

See Chapter 183.

**FOLLICULITIS**

Folliculitis, or superficial infection of the hair follicle, is most often caused by S. aureus (Bockhart impetigo). The lesions are typically small, discrete, dome-shaped pustules with an erythematous base, located at the ostium of the pilosebaceous canals (Fig. 665-10). Hair growth is unimpaired, and the lesions heal without scarring. Favorable sites include the scalp, buttocks, and extremities. Poor hygiene, maceration, drainage from wounds and abscesses, and shaving of the legs can be provocative factors. Folliculitis can also occur as a result of tar therapy or occlusive wraps. The moist environment encourages bacterial proliferation. In HIV-infected patients, S. aureus may produce confluent erythematous patches with satellite pustules in intertriginous areas and violaceous plaques composed of superficial follicular pustules in the scalp, axillae, or groin. The differential diagnosis include Candida, which may cause satellite follicular papules and pustules surrounding erythematous patches of intertrigo, and Malassezia furfur, which produces 2-3 mm, pruritic, erythematous, perifollicular papules and pustules on the back, chest, and extremities, particularly in patients who have diabetes mellitus or are taking corticosteroids or antibiotics.
Diagnosis is made by examining potassium hydroxide–treated scrapings from lesions. Detection of *Malassezia* may require a skin biopsy, demonstrating clusters of yeast and short, branching hyphae (“macaroni and meatballs”) in widened follicular ostia mixed with keratinous debris.

Topical antibiotic therapy (e.g., clindamycin 1% lotion or solution twice a day) is usually all that is needed for mild cases, but more severe cases may require use of a systemic antibiotic such as dicloxacillin or cephalaxin. Bacterial culture should be performed in treatment-resistant cases. In chronic recurrent folliculitis, daily application of a benzoyl peroxide 5% gel or wash may facilitate resolution.

**Folliculitis barbae (sycosis barbae)** is a deeper, more severe recurrent inflammatory form of folliculitis caused by *S. aureus* that involves the entire depth of the follicle. Erythematous follicular papules and pustules develop on the chin, upper lip, and angle of the jaw, primarily in young black males. Papules may coalesce into plaques, and healing may occur with scarring. Affected individuals are frequently found to be *S. aureus* carriers. Treatment with warm saline compresses and topical antibiotics such as mupirocin generally clears the infection. More extensive, recalcitrant cases may require therapy with β-lactamase-resistant systemic antibiotics for several weeks, and elimination of *S. aureus* from sites of carriage.

**Pseudomonal folliculitis (hot tub folliculitis)** is attributable to *P. aeruginosa*, predominantly serotype O-11. It occurs after exposure to poorly chlorinated hot tubs/whirlpools and swimming pools, as well as to a contaminated water slide, or loofah sponge. The lesions are pruritic papules and pustules or deeply erythematous to violaceous nodules that develop 8–48 hr after exposure and are most dense in areas covered by a bathing suit (Fig. 665-11). Patients occasionally experience fever, malaise, and lymphadenopathy. The organism is readily cultured from pus. The eruption usually resolves spontaneously in 1–2 wk, often leaving postinflammatory hyperpigmentation. Consideration should be given to use of systemic antibiotics (ciprofloxacin) in adolescent patients with constitutional symptoms. Immunocompromised children are susceptible to complications of *Pseudomonas* folliculitis (cellulitis) and should avoid hot tubs.

**FURUNCLES AND ABScesses**

**Etiology**
The causative agent in furuncles (“boils”) and carbuncles is usually *S. aureus*, which penetrates abraded perifollicular skin. Conditions predisposing to furuncle formation include obesity, hyperhidrosis, maceration, friction, and preexisting dermatitis. Furunculosis is also more common in individuals with low serum iron levels, diabetes, malnutrition, HIV infection, or other immunodeficiency states. Recurrent furunculosis is frequently associated with carriage of *S. aureus* in the nares, axillae, or perineum or close contact with someone such as a family member who is a carrier. Other bacteria or fungi may occasionally cause furuncles or carbuncles.

Community-acquired MRSA abscesses can also complicate folliculitis. Community-acquired MRSA infections commonly affect children and young adults, especially athletes where spread of the infection is enhanced by skin-to-skin contact. Infection can also be spread by overcrowding conditions, shared personal hygiene items, and a compromised skin barrier. They may occur in any location, however, they are most common on the lower abdomen, buttocks, and legs. Abscesses which are a common manifestation of community-acquired MRSA should be incised and drained. If oral antibiotics are needed, those with coverage against MRSA are recommended and commonly include oral trimethoprim-sulfamethoxazole (8–12 mg trimethoprim/kg/day in divided doses every 12 hr) or clindamycin (10–20 mg/kg/day in divided doses 3 times daily). To reduce colonization and hence reinfection, bleach baths for patients, and mupirocin intranasally in patients and in family members has been recommended.

**Clinical Manifestations**
This follicular lesion may originate from a preceding folliculitis or may arise initially as a deep-seated, tender, erythematous, perifollicular nodule. Although lesions are initially indurated, central necrosis and suppuration follow, leading to rupture and discharge of a central core of necrotic tissue and destruction of the follicle (Fig. 665-12). Healing occurs with scar formation. Sites of predilection are the hair-bearing areas on the face, neck, axillae, buttocks, and groin. Pain may be intense if the lesion is situated in an area where the skin is relatively fixed, such as in the external auditory canal or over the nasal cartilages. Patients with furuncles usually have no constitutional symptoms; bacteremia may occasionally ensue. Rarely, lesions on the upper lip or cheek may lead to cavernous sinus thrombosis. Infection of a group of contiguous follicles, with multiple drainage points, accompanied by inflammatory changes in surrounding connective tissue is a carbuncle. Carbuncles may be accompanied by fever, leukocytosis, and bacteremia.

**Treatment**
Treatment for furuncle and carbuncle includes regular bathing with antimicrobial soaps (chlorhexidine) and wearing of loose-fitting clothing to minimize predisposing factors for furuncle formation. Frequent application of a hot, moist compress may facilitate drainage of lesions. Large lesions may be drained by a small incision. Carbuncles and large or numerous furuncles should be treated with systemic antibiotics chosen on the basis of culture and sensitivity testing results.

**Pitted Keratolysis**
Pitted keratolysis occurs most frequently in humid tropical and subtropical climates, particularly in individuals whose feet are moist for prolonged periods, for example, as a result of hyperhidrosis, prolonged wearing of boots, or immersion in water. It occurs most commonly in young males from early adolescence to the late 20s. The lesions consist
biopsy, which reveals the Gram-positive organisms, and culture. The treatment of choice is parenteral penicillin or erythromycin.

**TUBERCULOSIS OF THE SKIN**

See Chapters 215 and 217. Cutaneous tuberculosis infection occurs worldwide, particularly in association with HIV infection, malnutrition, and poor sanitary conditions. Primary cutaneous tuberculosis is rare in the United States. All forms of cutaneous disease are caused by Mycobacterium tuberculosis, Mycobacterium bovis, and occasionally by the bacillus Calmette-Guérin (BCG), an attenuated vaccine form of M. bovis. The manifestations caused by a given organism are indistinguishable from one another. After invasion of the skin, mycobacteria either multiply intracellularly within macrophages, leading to progressive disease, or are controlled by the host immune reaction.

Primary cutaneous tuberculosis (tuberculous chancre) results when *M. tuberculosis* or *M. bovis* gains access to the skin or mucous membranes through trauma in a previously uninfected individual without immunity to the organism. Sites of predilection are the face, lower extremities, and genitals. The initial lesion develops 2–4 wk after introduction of the organism into the damaged tissue. A red-brown papule gradually enlarges to form a shallow, firm, sharply demarcated ulcer. Satellite abscesses may be present. Some lesions acquire a crust resembling impetigo, and others become heaped up and verrucous at the margins. The primary lesion can also manifest as a painless ulcer on the conjunctiva, gingiva, or palate and occasionally as a painless acute paronychia. Painless regional adenopathy may appear several weeks after the development of the primary lesion and may be accompanied by lymphangitis, lymphadenitis, or perforation of the skin surface, forming *scrofuloderma*. Untreated lesions heal with scarring within 12 mo but may reactivate, may form lupus vulgaris, or, rarely, may progress to the acute miliary form. Therefore, antituberculous therapy is indicated (see Chapter 215).

*M. tuberculosis* or *M. bovis* can be cultured from the skin lesion and local lymph nodes, but acid-fast staining of histologic sections, particularly of a well-controlled infection, often does not reveal the organism. The differential diagnosis is broad, including a syphilitic chancre; deep fungal or atypical mycobacterial infection; leprosy; tularemia; and hidradenitis suppurativa. The course is indolent, and constitutional symptoms are typically absent. Antituberculous therapy is indicated (see Chapter 215).

Direct cutaneous inoculation of the tubercle bacillus into a previously infected individual with a moderate to high degree of immunity initially produces a small papule with surrounding inflammation. **Tuberculosis verrucosa cutis** (warty tuberculosis) forms when the papule becomes hyperkeratotic and warty, and several adjacent papules coalesce or a single papule expands peripherally to form a brownish red to violaceous, exudative, crusty verrucous plaque. Irregular extension of the margins of the plaque produces a serpiginous border. Children have the lesions most commonly on the lower extremities after Direct cutaneous inoculation of the tubercle bacillus into a previously infected individual with a moderate to high degree of immunity initially produces a small papule with surrounding inflammation. **Tuberculosis verrucosa cutis** (warty tuberculosis) forms when the papule becomes hyperkeratotic and warty, and several adjacent papules coalesce or a single papule expands peripherally to form a brownish red to violaceous, exudative, crusty verrucous plaque. Irregular extension of the margins of the plaque produces a serpiginous border. Children have the lesions most commonly on the lower extremities after trauma and contact with infected material such as sputum or soil. Regional lymph nodes are involved only rarely. Spontaneous healing with atrophic scarring takes place over months to years. Healing is also gradual with antituberculous therapy.

**Lupus vulgaris** is a rare, chronic, progressive form of cutaneous tuberculosis that develops in individuals with a moderate to high
degree of tuberculin sensitivity induced by previous infection. The incidence is greater in cool, moist climates, particularly in females. Lupus vulgaris develops as a result of direct extension from underlying joints or lymph nodes; through lymphatic or hematogenous spread; or, rarely, by cutaneous inoculation with BCG vaccine. It most commonly follows cervical adenitis or pulmonary tuberculosis. Approximately 33% of cases are preceded by scrofuloderma, and 90% of cases manifest on the head and neck, most commonly on the nose or cheek. Involvement of the trunk is uncommon. A typical solitary lesion consists of a soft, brownish red papule that has an apple-jelly color when examined by dissection. Peripheral expansion of the papule or, occasionally, the coalescence of several papules forms an irregular lesion of variable size and form. One or several lesions may develop, including nodules or plaques that are flat and serpiginous, hypertrophic and verrucous, or edematous in appearance. Spontaneous healing occurs centrally, and lesions characteristically reappear within the area of atrophy. Chronicity is characteristic, and persistence and progression of plaques over many years is common. Lymphadenitis is present in 40% of those with lupus vulgaris, and 10-20% has infection of the lungs, bones, or joints. Extensive deformities may be caused by vegetative masses and ulceration involving the nasal, buccal, or conjunctival mucosa; the palate; the gingiva; or the oropharynx. Squamous cell carcinoma, with a relatively high metastatic potential, may develop, usually after several years of the disease. After a temporary impairment in immunity, particularly after measles infection (lupus exanthematicus), multiple lesions may form at distant sites as a result of hematogenous spread from a latent focus of infection. The histopathology reveals a tuberculoid granuloma without caseation; organisms are extremely difficult to demonstrate. The differential diagnosis includes sarcoidosis, atypical mycobacterial infection, blastomyosomycosis, chromoblastomycosis, actinomycosis, leishmaniasis, tertiary syphilis, leprosy, hypertrophic lichen planus, psoriasis, lupus erythematosus, lichen planus, and Bowen disease. Small lesions can be excised. Antituberculous drug therapy usually halts further spread and induces involution.

**Orificial tuberculosis** (tuberculosis cutis orificialis) appears on the mucous membranes and periorificial skin after autoinoculation of mycobacteria from sites of progressive infection. It is a sign of advanced internal disease and carries a poor prognosis and occurs in sensitized host with impaired cellular immunity. Lesions appear as painful, yellowish or red nodules that form punched-out ulcers with inflammation and edema of the surrounding mucosa. Treatment consists of identification of the source of infection and initiation of antituberculosis therapy.

**Miliary tuberculosis** (hematogenous primary tuberculosis) rarely manifests cutaneously and occurs most commonly in infants and in individuals who are immunosuppressed after chemotherapy or infection with measles or HIV. The eruption consists of crops of symmetrically distributed, minute, erythematous to purpuric macules, papules, or vesicles. The lesions may ulcerate, drain, crust, and form sinus tracts or may form subcutaneous gummas, especially in malnourished children with impaired immunity. Constitutional signs and symptoms are common, and a leukemoid reaction or aplastic anemia may develop. Tubercle bacilli are readily identified in an active lesion. A fulminant course should be anticipated, and aggressive antituberculous therapy is indicated.

Single or multiple metastatic tuberculous abscesses (tuberculous gummas) may develop on the extremities and trunk by hematogenous spread from a primary focus of infection during a period of decreased immunity, particularly in malnourished and immunosuppressed children. The fluent, nontender, erythematous subcutaneous nodules may ulcerate and form fistulas.

**Vaccination with BCG** characteristically produces a papule approximately 2 wk after vaccination. The papule expands in size, typically ulcerates within 2-4 mo, and heals slowly with scarring. In 1-2 per million vaccinations, a complication caused specifically by the BCG organism occurs, including regional lymphadenitis, lupus vulgaris, scrofuloderma, and subcutaneous abscess formation.

**Tuberculids** are skin reactions that exhibit tuberculoid features histologically but do not contain detectable mycobacteria. The lesions appear in a host who usually has moderate to strong tuberculin reactivity, has a history of previous tuberculosis of other organs, and usually shows a therapeutic response to antituberculous therapy. The cause of tuberculids is poorly understood. Most affected patients are in good health with no clear focus of disease at the time of the eruption. The most commonly observed tuberculid is the papulonecrotic tuberculid. Recurrent crops of symmetrically distributed, asymptomatic, firm, sterile, dusky-red papules appear on the extensor aspects of the limbs, the dorsum of the hands and feet, and the buttocks. The papules may undergo central ulceration and eventually heal, leaving sharply delineated, circular, depressed scars. The duration of the eruption is variable, but it usually disappears promptly after treatment of the primary infection. Lichen scrofulosorum, another form of tuberculid, is characterized by asymptomatic, grouped, pinhead-sized, often follicular pink or red papules that form discoid plaques, mainly on the trunk. Healing occurs without scarring.

**Atypical mycobacterial** infection may cause cutaneous lesions in children. *Mycobacterium marinum* is found in saltwater, freshwater, and diseased fish. In the United States, it is most commonly acquired from tropical fish tanks and swimming pools. Traumatic abrasion of the skin serves as a portal of entry for the organism. Approximately 3 wk after inoculation, a single reddish papule develops and enlarges slowly to form a violaceous nodule or, occasionally, a warty plaque (Fig. 665-14). The lesion occasionally breaks down to form a crusted ulcer or a suppuring abscess. Sporotrichoid erythematous nodules along lymphatics may also suppurate and drain. Lesions are most common on the elbows, knees, and feet of swimmers, and on the hands and fingers in persons with aquarium-acquired infection. Systemic signs and symptoms are absent. Regional lymph nodes occasionally become slightly enlarged but do not break down. Rarely, the infection becomes disseminated, particularly in an immunosuppressed host. A biopsy specimen of a fully developed lesion demonstrates a granulomatous infiltrate with tuberculoid architecture. Treatment options include tetracycline, doxycycline, minocycline, clarithromycin, and rifampin plus ethambutol. Application of heat to the affected site may be a useful adjunctive therapy (see Chapter 217).

*Mycobacterium kansasi* primarily causes pulmonary disease; skin disease is rare, often occurring in an immunocompromised host. Most commonly, sporotrichoid nodules develop after inoculation of traumatized skin. Lesions may develop into ulcerated, crusted, or verrucous plaques. The organism is relatively sensitive to antituberculous medications, which should be chosen on the basis of susceptibility testing.

*Mycobacterium scrofulaceum* causes cervical lymphadenitis (scrofuloderma) in young children, typically in the submandibular region. Nodes enlarge over several weeks, ulcerate, and drain. The local reaction is nontender and circumscribed, constitutional symptoms are absent, and there generally is no evidence of lung or other organ involvement. Other atypical mycobacteria may cause a similar condition. The differential diagnosis includes tuberculosis, lymphogranuloma venereum, syphilis, leprosy, and chromoblastomycosis.

Figure 665-14 Violaceous, warty plaque of *Mycobacterium marinum* infection.
presentation, including *Mycobacterium avium* complex, *Mycobacterium kansasii*, and *Mycobacterium fortuitum*. **Treatment** is accomplished by excision and administration of antituberculous drugs (see Chapter 217).

*Mycobacterium ulcerans* (Buruli ulcer) causes a painless subcutaneous nodule after inoculation of abraded skin. Most infections occur in children in tropical rain forests. The nodule usually ulcerates, develops undermined edges, and may spread over large areas, most commonly on an extremity. Local necrosis of subcutaneous fat, producing a septal panniculitis, is characteristic. Ulcers persist for months to years before healing spontaneously with scarring and sometimes with lymphedema. Constitutional symptoms and lymphadenopathy are absent. Diagnosis is made by culturing the organism at 32-33°C (89.6-91.4°F). **Treatment of choice** is early excision of the lesion. Local heat therapy and oral chemotherapy may benefit some patients.

*M. avium* complex, composed of more than 20 subtypes, most commonly causes chronic pulmonary infection. Cervical lymphadenitis and osteomyelitis occur occasionally, and papules or purulent leg ulcers occur rarely by primary inoculation. Skin lesions may be an early sign of disseminated infection. The lesions may take various forms, including erythematous papules, pustules, nodules, abscesses, ulcers, panniculitis, and sporotrichoid spread along lymphatics. For treatment, see Chapter 217.

*M. fortuitum* complex causes disease in an immunocompetent host principally by primary cutaneous inoculation after traumatic injury, injection, or surgery. A nodule, abscess, or cellulitis develops 4-6 wk after inoculation. In an immunocompromised host, numerous subcutaneous nodules may form, break down, and drain. **Treatment** is based on identification and susceptibility testing of the organism.

*Bibliography is available at Expert Consult.*
Bibliography


TINEA VERSICOLOR

A common, innocuous, chronic fungal infection of the stratum corneum, tinea versicolor is caused by the dimorphic yeast *Malassezia globosa*. The synonyms *Pityrosporum ovale* and *Pityrosporum orbiculare* were used previously to identify the causal organism.

**Etiology**

*M. globosa* is part of the indigenous flora, predominantly in the yeast form, and is found particularly in areas of skin that are rich in sebum production, and is part of normal skin flora. Proliferation of filamentous forms occurs in the disease state. Predisposing factors include a warm, humid environment, excessive sweating, occlusion, high plasma cortisol levels, immunosuppression, malnourishment, and genetically determined susceptibility. The disease is most prevalent in adolescents and young adults.

**Clinical Manifestations**

The lesions of tinea versicolor vary widely in color. In white individuals, they are typically reddish brown, whereas in black individuals they may be either hypopigmented or hyperpigmented. The characteristic macules are covered with a fine scale. They often begin in a perifollicular location, enlarge, and merge to form confluent patches, most commonly on the neck, upper chest, back, and upper arms (Fig. 666-1). Facial lesions are common in adolescents; lesions occasionally appear on the forearms, dorsum of the hands, and pubis. There may be little or no pruritus. Involved areas do not tan after sun exposure. A papulopustular perifollicular variant of the disorder may occur on the back, chest, and sometimes the extremities.

**Differential Diagnosis**

Examination with a Wood lamp discloses a yellowish gold fluorescence. A potassium hydroxide (KOH) preparation of scrapings is diagnostic, demonstrating groups of thick-walled spores and myriad short, thick, angular hyphae resembling macaroni/spaghetti and meatballs. Skin biopsy, including culture and special stains for fungi (periodic acid–Schiff), are often necessary to make the diagnosis in cases of primarily follicular involvement. Microscopically, organisms and keratinous debris can be seen within dilated follicular ostia.

Tinea versicolor must be distinguished from dermatophyte infections, seborrheic dermatitis, pityriasis alba, and secondary syphilis. Tinea versicolor may mimic nonscaling pigmentary disorders, such as postinflammatory pigmentary change, if a patient has removed the scales by scrubbing. *M. globosa* folliculitis must be distinguished from the other forms of folliculitis.

**Treatment**

Many therapeutic agents can be used to treat this disease successfully. The causative agent, a normal human saprophyte, is not eradicated from the skin, however, and the disorder recurs in predisposed individuals. Appropriate topical therapy may include 1 of the following: selenium 2% shampoo applied for 10 minutes before rinsing for 2 wk; ketoconazole 2% shampoo 3 times a wk for a month or a single application daily for 3 days; and terbinafine spray once to twice daily for 1-2 wk. Antifungal creams are available and can be used; however, these can be impractical to apply given the large surface of skin involved. Oral therapy may be more convenient and may be achieved successfully with ketoconazole or fluconazole, 400 mg, repeated in 1 wk, or itraconazole, 200 mg/24 hr for 5-7 days. Recurrent episodes continue to respond promptly to these agents. Oral therapy is particularly helpful in those with severe disease or recurrent disease, or in those where topical therapies have failed. Maintenance therapy with selenium sulfide shampoo or ketoconazole 2% shampoo once a week may be used.

**DERMATOPHYTOSES**

Dermatophytoses are caused by a group of closely related filamentous fungi with a propensity for invading the stratum corneum, hair, and nails. The 3 principal genera responsible for infections are *Trichophyton*, *Microsporum*, and *Epidermophyton*. 
Etiology

*Trichophyton* spp. cause lesions of all keratinized tissue, including skin, nails, and hair. *Trichophyton rubrum* is the most common dermatophyte pathogen. *Microsporum* spp. principally invade the hair, and the *Epidermophyton* spp. invade the intertriginous skin. Dermatophyte infections are designated by the word *tinea* followed by the Latin word for the anatomic site of involvement. The dermatophytes are also classified according to source and natural habitat. Fungi acquired from the soil are called geophilic. They infect humans sporadically, inciting an inflammatory reaction. Dermatophytes that are acquired from animals are zoophilic. Transmission may be through direct contact or indirectly by infected animal hair or clothing. Infected animals are frequently asymptomatic. Dermatophytes acquired from humans are referred to as anthropophilic. These infestations range from chronic low-grade to acute inflammatory disease. *Epidermophyton* infections are transmitted only by humans, but various species of *Trichophyton* and *Microsporum* can be acquired from both human and nonhuman sources.

Epidemiology

Host defense has an important influence on the severity of the infection. Disease tends to be more severe in individuals with diabetes mellitus, lymphoid malignancies, immunosuppression, and states with high plasma cortisol levels, such as Cushing syndrome. Some dermatophytes, most notably the zoophilic species, tend to elicit more severe, suppressive inflammation in humans. Some degree of resistance to reinfection is acquired by most infected persons and may be associated with a delayed hypersensitivity response. No relationship has been demonstrated, however, between antibody levels and resistance to infection. The frequency and severity of infection are also affected by the geographic locale, the genetic susceptibility of the host, and the virulence of the strain of dermatophyte. Additional local factors that predispose to infection include trauma to the skin, hydration of the skin with maceration, occlusion, and elevated temperature.

Occasionally, a secondary skin eruption, referred to as a dermatophytid or "id" reaction, appears in sensitized individuals and has been attributed to circulating fungal antigens derived from the primary infection. The eruption is characterized by grouped papules (Fig. 666-2) and vesicles and, occasionally, by sterile pustules. Symmetric articular lesions and a more generalized maculopapular eruption also can occur. Id reactions are most often associated with tinea pedis but also occur with tinea capitis.

**Tinea Capitis Clinical Manifestations**

Tinea capitis is a dermatophyte infection of the scalp most often caused by *Trichophyton tonsurans*, occasionally by *Microsporum canis*, and, much less commonly, by other *Microsporum* and *Trichophyton* spp. It is particularly common in black children age 4-14 yr. In *Microsporum* and some *Trichophyton* infections, the spores are distributed in a sheath-like fashion around the hair shaft (ectothrix infection), whereas *T. tonsurans* produces an infection within the hair shaft (endothrix). *Endothrix* infections may continue past the anagen phase of hair growth into telogen and are more chronic than infections with ectothrix organisms that persist only during the anagen phase. *T. tonsurans* is an anthropophilic species acquired most often by contact with infected hairs and epithelial cells that are on such surfaces as theater seats, hats, and combs. Dermatophyte spores may also be airborne within the immediate environment, and high carriage rates have been demonstrated in noninfected schoolmates and household members. *M. canis* is a zoophilic species that is acquired from cats and dogs.

The clinical presentation of tinea capitis varies with the infecting organism. Endothrix infections such as those caused by *T. tonsurans* create a pattern known as “black-dot ringworm,” characterized initially by many small circular patches of alopecia in which hairs are broken off close to the hair follicle (Fig. 666-3). Another clinical variant manifests as diffuse scaling, with minimal hair loss secondary. It strongly resembles seborrheic dermatitis, psoriasis, or atopic dermatitis (Fig. 666-4). *T. tonsurans* may also produce a chronic and more diffuse alopecia. Lymphadenopathy is common (Fig. 666-5). A severe inflammatory response produces elevated, boggy granulomatous masses (kerions), which are often studded with pustules (Fig. 666-6A). Fever, pain, and regional adenopathy are common, and permanent scarring and alopecia may result (Fig. 666-6B). The zoophilic organism *M. canis* or the geophilic organism *Microsporum gypseum* also may cause kerion formation. The pattern produced by *Microsporum audouinii*, the most

![Figure 666-2](image1)

**Figure 666-2** Id reaction. Papular eruption of the face associated with severe tinea infection of the hand.

![Figure 666-3](image2)

**Figure 666-3** Black-dot ringworm with hairs broken off at the scalp.

![Figure 666-4](image3)

**Figure 666-4** Tinea capitis mimicking seborrheic dermatitis.
common cause of tinea capitis in the 1940s and 1950s, is characterized initially by a small papule at the base of a hair follicle. The infection spreads peripherally, forming an erythematous and scaly circular plaque (ringworm) within which the infected hairs become brittle and broken. Numerous confluent patches of alopecia develop, and patients may complain of severe pruritus. M. audouinii infection is no longer common in the United States. Favus is a chronic form of tinea capitis that is rare in the United States and is caused by the fungus Trichophyton schoenleini. Favus starts as yellowish red papules at the opening of hair follicles. The papules expand and coalesce to form cup-shaped, yellowish, crusted patches that fluoresce dull green under a Wood lamp.

Differential Diagnosis
Tinea capitis can be confused with seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania, and certain dystrophic hair disorders. When inflammation is pronounced, as in kerion, primary or secondary bacterial infection must also be considered. In adolescents, the patchy, moth-eaten type of alopecia associated with secondary syphilis may resemble tinea capitis. If scarring occurs, discoid lupus erythematosus and lichen planopilaris must also be considered in the differential diagnosis.

The important diagnostic procedures for the various dermatophyte diseases include examination of infected hairs with a Wood lamp, microscopic examination of KOH preparations of infected material, and identification of the etiologic agent by culture. Hairs infected with common *Microsporum* spp. fluoresce a bright blue-green. Most *Trichophyton*-infected hairs do not fluoresce.

Microscopic examination of a KOH preparation of infected hair from the active border of a lesion discloses tiny spores surrounding the hair shaft in *Microsporum* infections and chains of spores within the hair shaft in *T. tonsurans* infections. Fungal elements are not usually seen in scales. A specific etiologic diagnosis of tinea capitis may be obtained by planting broken off infected hairs on Sabouraud medium with reagents to inhibit growth of other organisms. Such identification may require 2 wk or more.

Treatment
Oral administration of griseofulvin microcrystalline (20-25 mg/kg/24 hr, or 10-15 mg/kg per day if the ultramicrsize form is used) is the recommended treatment for all forms of tinea capitis. Absorption of griseofulvin is enhanced by ingestion of a fatty meal and should be recommended for the patient. It may be necessary for 8-12 wk and should be terminated only after fungal culture results are negative. Treatment for 1 mo after a negative culture result minimizes the risk of recurrence. Adverse reactions to griseofulvin are rare but include nausea, vomiting, headache, blood dyscrasias, phototoxicity, and hepatotoxicity. Terbinafine is also effective at a dosage of 3-6 mg/kg/24 hr for 4-6 wk or possibly in pulse therapy, although it has limited activity against *M. canis*. The oral granules formulation of terbinafine is approved by the FDA for tinea capitis in children 4 yr of age and older. Oral itraconazole is useful in instances of griseofulvin resistance, intolerance, or allergy. Itraconazole is given for 4-6 wk at a dosage of 3-5 mg/kg/24 hr with food. Capsules are preferable to the syrup, which may cause diarrhea. Itraconazole is not approved by the FDA for treatment of dermatophyte infections in the pediatric population. Topical therapy alone is ineffective, but it may be an important adjunct because it may decrease the shedding of spores, and should be recommended in all patients. Asymptomatic dermatophyte carriage in family members is common. Because 1 in 3 families have at least 1 member who is a carrier, treatment of both patient and potential carriers with a sporidical shampoo may hasten clinical resolution. Vigorous shampooing with a 2.5% selenium sulfide, zinc pyrithione, or ketoconazole shampoo is helpful. It is not necessary to shave the scalp.

Tinea Corporis
Clinical Manifestations
Tinea corporis, defined as infection of the glabrous skin, excluding the palms, soles, and groin, can be caused by most of the dermatophyte species, although *T. rubrum* and *Trichophyton mentagrophytes* are the most prevalent etiologic organisms. In children, infections with *M. canis* are also common. Tinea corporis can be acquired by direct contact with infected persons or by contact with infected scales or hairs deposited on environmental surfaces. *M. canis* infections are usually acquired from infected pets.

The most typical clinical lesion begins as a dry, mildly erythematous, elevated, scaly papule or plaque that spreads centripetally and clears centrally to form the characteristic annular lesion responsible for the designation ringworm (Fig. 666-7). At times, plaques with advancing borders may spread over large areas. Grouped pustules are another variant. Most lesions clear spontaneously within several months, but some may become chronic. Cental clearing does not always occur (Fig. 666-8), and differences in host response may result in wide variability in the clinical appearance—for example, granulomatous lesions called Majocchi granuloma, which are caused by penetration of organisms along the hair follicle to the level of the dermis, produce a fungal folliculitis and perifolliculitis (Fig. 666-9), and the kerion-like lesions referred to as tinea profunda. Majocchi granuloma is more..
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psoriasis, seborrheic dermatitis, erythema chronicum migrans, and tinea versicolor. Microscopic examination of KOH wet mount preparations and cultures should always be performed when fungal infection is considered. Tinea corporis usually does not fluoresce with a Wood lamp.

**Treatment**

Tinea corporis usually responds to treatment with one of the topical antifungal agents (e.g., imidazoles, terbinafine, naftifine) twice daily for 2-4 wk. In unusually severe or extensive disease, a course of therapy with oral griseofulvin microcrystalline may be required for 4 wk. Itraconazole has produced excellent results in many cases with a 1-2 wk course of oral therapy. Combination topical corticosteroid/antifungal preparations should not be used as it may result in worsening or persistent infection.

**Tinea Cruris**

**Clinical Manifestations**

Tinea cruris, or infection of the groin, occurs most often in adolescent males and is usually caused by the anthropophilic species *Epidermophyton floccosum* or *T. rubrum*, but occasionally by the zoophilic species *T. mentagrophytes*.

The initial clinical lesion is a small, raised, scaly, erythematous patch on the inner aspect of the thigh. This spreads peripherally, often developing numerous tiny vesicles at the advancing margin. It eventually forms bilateral, irregular, sharply bordered patches with hyperpigmented scaly centers. In some cases, particularly in infections with *T. mentagrophytes*, the inflammatory reaction is more intense and the infection may spread beyond the crural region. The scrotum and labia are usually not involved in the infection, an important distinction from candidosis. Pruritus may be severe initially but abates as the inflammatory reaction subsides. Bacterial superinfection may alter the clinical appearance, and erythrasma or candidosis may coexist. Tinea cruris is more prevalent in obese persons and in persons who perspire excessively and wear tight-fitting clothing.

**Differential Diagnosis**

The diagnosis of tinea cruris is confirmed by culture and by demonstration of septate hyphae on a KOH preparation of epidermal scrapings. The disorder must be differentiated from intertrigo, allergic contact dermatitis, candidosis, and erythrasma. Bacterial superinfection must be precluded when there is a severe inflammatory reaction.

**Treatment**

Patients should be advised to wear loose cotton underwear. **Topical treatment** with an imidazole twice a day for 3-4 wk is recommended for severe infection, especially because these agents are effective in mixed candidal-dermatophytic infections.

**Tinea Pedis**

**Clinical Manifestations**

Tinea pedis (athlete’s foot), infection of the toe webs and soles of the feet, is uncommon in young children but occurs with some frequency in preadolescent and adolescent males. The usual etiologic agents are *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*.

Most commonly, the lateral toe webs (3rd to 4th and 4th to 5th interdigital spaces) and the subdigital crevice are fissured, with maceration and peeling of the surrounding skin (Fig. 666-10). Severe tenderness, itching, and a persistent foul odor are characteristic. These lesions may become chronic. This type of infection may involve overgrowth by bacterial flora, including *Kytococcus sedentarius*, *Brevibacterium epidermidis*, and Gram-negative organisms. Less commonly, a chronic diffuse hyperkeratosis of the sole of the foot occurs with only mild erythema (Fig. 666-11). In many cases, 2 feet and 1 hand are involved. This type of infection is more refractory to treatment and tends to recur. An inflammatory vesicular type of reaction may occur with *T. mentagrophytes* infection. This type is most common in young children. The lesions involve any area of the foot, including the dorsal surface, and are usually circumscribed. The initial papules progress to

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**Figure 666-7** Annular plaque of tinea corporis with central clearing.

**Figure 666-8** Minimal central clearing with tinea corporis.

**Figure 666-9** Follicular papule and pustule in Majocchi granuloma after use of a superpotent topical steroid.

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common after inappropriate treatment with topical corticosteroids, especially the superpotent class.

**Differential Diagnosis**

Many skin lesions, both infectious and noninfectious, must be differentiated from the lesions of tinea corporis. Those most frequently confused are granuloma annulare, nummular eczema, pityriasis rosea,
Cutaneous Fungal Infections

Chapter 666

Tinea Unguium
Clinical Manifestations
Tinea unguium (onychomycosis) is a dermatophyte infection of the nail plate. It occurs most often in patients with tinea pedis, but it may occur as a primary infection. It can be caused by a number of dermatophytes, of which T. rubrum and T. mentagrophytes are the most common.

Differential Diagnosis
Tinea unguium must be differentiated from various dystrophic nail disorders. Changes as a result of trauma, psoriasis, lichen planus, eczema, and trachyonychia can all be confused with tinea unguium. Nails infected with C. albicans have several distinguishing features; most prominently, a pronounced paronychial swelling. Thin shavings taken from the infected nail, preferably from the deeper areas, should be examined microscopically with KOH and cultured. Repeated attempts may be required to demonstrate the fungus. Histologic evaluation of nail clippings with special stains for dermatophytes can be diagnostic.

The long half-life of itraconazole in the nail has led to promising trials of intermittent short courses of therapy (double the normal dose for 1 wk of each mo for 3-4 mo). Oral terbinafine is also used for the...
treatment of onychomycosis. Terbinafine once daily for 12 wk is more effective than itraconazole pulse therapy. Griseofulvin and application of topical fungistatic agents to the nail bed are often ineffective and are not recommended.

Tinea Nigra Palmaris

Tinea nigra palmaris is a rare but distinctive superficial fungal infection that occurs principally in children and adolescents. It is caused by the dimorphic fungus Phaeoannellomyces werneckii, which imparts a gray-black color to the affected palm. The characteristic lesion is a well-defined hyperpigmented macule. Scaling and erythema are rare, and the lesions are asymptomatic. Tinea nigra is often mistaken for a junctional nevus, melanoma, or staining of the skin by contactants. Treatment with an imidazole antifungal.

### Table 666-1 Primary Immunodeficiencies Underlying Fungal Infections

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ASSOCIATED INFECTIONS</th>
<th>IMMUNOLOGIC PHENOTYPE</th>
<th>GENE, TRANSMISSION</th>
</tr>
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<tbody>
<tr>
<td>CMC SCID</td>
<td>Bacteria, viruses, fungi, mycobacteria</td>
<td>No T cells, with or without B and/or NK cell lymphopenia</td>
<td>&gt;30 genes: IL2RG, X-linked; JAK3, autosomal recessive; RAG1, autosomal recessive; RAG2, autosomal recessive; ARTEMIS, autosomal recessive; ADA, autosomal recessive; CD3, autosomal recessive, etc.</td>
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<td>MHC class II deficiency</td>
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<td>CD4 T cells &lt;300 cells/mm³</td>
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<td>Hyperimmunoglobulin E, deficit of interleukin-17–producing T cells</td>
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<td>S. aureus</td>
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<td>Impaired interleukin-17F, interleukin-17A/F function</td>
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<td>STAT1 GOF mutations</td>
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CANDIDAL INFECTIONS (CANDIDOsis, CANDIDIASIS, AND MONILIASIS)

See Chapter 234.

The dimorphic yeasts of the genus Candida are ubiquitous in the environment, but C. albicans usually causes candidosis in children. This yeast is not part of the indigenous skin flora, but it is a frequent transient on skin and may colonize the human alimentary tract and the vagina as a saprophytic organism. Certain environmental conditions, notably elevated temperature and humidity, are associated with an increased frequency of isolation of C. albicans from the skin. Many bacterial species inhibit the growth of C. albicans, and alteration of normal flora by the use of antibiotics may promote overgrowth of the yeast.

Chronic mucocutaneous candidiasis is associated with a diverse group of primary immunodeficiency diseases (Table 666-1). Chronic
mucocutaneous candidiasis is characterized by chronic or recurrent *Candida* infections of the oral cavity, esophagus, genitals, nails, and skin. Chronic mucocutaneous candidiasis may also be seen as an acquired infection in patients with HIV infection, and during immunosuppressive treatments.

**Oral Candidosis (Thrush)**

See Chapter 234.

**Vaginal Candidosis**

See Chapters 120 and 234.

*C. albicans* is an inhabitant of the vagina in 5-10% of women, and vaginal candidosis is not uncommon in adolescent girls. A number of factors can predispose to this infection, including antibiotic therapy, corticosteroid therapy, diabetes mellitus, pregnancy, and the use of oral contraceptives. The infection manifests as cheesy white plaques on an erythematous vaginal mucosa and a thick white-yellow discharge. The disease may be relatively mild or may produce pronounced inflammation and scaling of the external genitals and surrounding skin with progression to vesiculation and ulceration. Patients often complain of severe itching and burning in the vaginal area. Before treatment is initiated, the diagnosis should be confirmed by microscopic examination and/or culture. The infection may be eradicated by insertion of nystatin or imidazole vaginal tablets, suppositories, creams, or foam. If these products are ineffective, the addition of one dose of fluconazole (150 mg) is effective.

**Congenital Cutaneous Candidosis**

See Chapter 234.

**Candidal Diaper Dermatitis**

Candidal diaper dermatitis is a ubiquitous problem in infants and, although relatively benign, is often frustrating because of its tendency to recur. Predisposed infants usually carry *C. albicans* in their intestinal tracts, and the warm, moist, occluded skin of the diaper area provides an optimal environment for its growth. A seborrheic, atopic, or primary irritant contact dermatitis usually provides a portal of entry for the yeast.

The primary clinical manifestation consists of an intensely erythematous, confluent plaque with a scalloped border and a sharply demarcated edge. It is formed by the confluence of numerous papules and vesicular pustules. Satellite pustules, those that stud the contiguous skin, are a hallmark of localized candidal infections. The perianal skin, inguinal folds, perineum, and lower abdomen are usually involved (Fig. 666-14). In males, the entire scrotum and penis may be involved, with an erosive balanitis of the perimeatal skin. In females, the lesions may be found on the vaginal mucosa and labia. In some infants, the process is generalized, with erythematous lesions distant from the diaper area. In some cases, the generalized process may represent a fungal id (hypersensitivity) reaction.

The **differential diagnosis** of candidal diaper dermatitis includes other eruptions of the diaper area that may coexist with candidal infection. For this reason, it is important to establish a diagnosis by means of KOH preparation or culture.

**Treatment** consists of applications of an imidazole cream 2 times daily. The combination of a corticosteroid and an antifungal agent may be justified if inflammation is severe but may confuse the situation if the diagnosis is not firmly established. Corticosteroid should not be continued for more than a few days. Protection of the diaper area by an application of thick zinc oxide paste overlying the antifungal preparation may be helpful. The paste is more easily removed with mineral oil than with soap and water. Fungal id reactions gradually abate with successful treatment of the diaper dermatitis or may be treated with a mild corticosteroid preparation. When recurrences of diaper candidosis are frequent, it may be beneficial to prescribe a course of oral antifungal therapy to decrease the yeast population in the gastrointestinal tract. Some infants seem to be receptive hosts for *C. albicans* and may reacquire the organism from a colonized adult.

**Intertriginous Candidosis**

Intertriginous candidosis occurs most often in the axillae and groin, on the neck (Fig. 666-15) under the breasts, under pendulous abdominal fat folds, in the umbilicus, and in the glutal cleft. Typical lesions are large, confluent areas of moist, denuded, erythematous skin with an irregular, macerated, scaly border. Satellite lesions are characteristic and consist of small vesicles or pustules on an erythematous base. With time, intertriginous candidal lesions may become lichenified, dry, scaly plaques. The lesions develop on skin subjected to irritation and maceration. Candidal superinfection is more likely to occur under conditions that lead to excessive perspiration, especially in obese children and in children with underlying disorders, such as diabetes mellitus. A similar condition, interdigital candidosis, commonly occurs in individuals whose hands are constantly immersed in water. Fissures occur between the fingers and have red denuded centers, with an overhanging white epithelial fringe. Similar lesions between the toes may be secondary to occlusive footwear. Treatment is the same as for other candidal infections.

**Perianal Candidosis**

Perianal dermatitis develops at sites of skin irritation as a result of occlusion, constant moisture, poor hygiene, anal fissures, and pruritus from pinworm infestation. It may become superinfected with *C. albicans*, especially in children who are receiving oral antibiotic or corticosteroid medication. The involved skin becomes erythematous, macerated, and excoriated, and the lesions are identical to those of candidal intertrigo or candidal diaper rash. Application of a topical

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**Figure 666-14** Erythematous confluent plaque caused by candidal infection.

**Figure 666-15** Intertriginous candidosis of the neck.
antifungal agent in conjunction with improved hygiene is usually effective. Underlying disorders such as pinworm infection must also be treated (see Chapter 293).

**Candidal Paronychia and Onychia**
See Chapter 663.

**Candidal Granuloma**
Candidal granuloma is a rare response to an invasive candidal infection of skin. The lesions appear as crusted, verrucous plaques and hornlike projections on the scalp, face, and distal limbs. Affected patients may have single or numerous defects in immune mechanisms, and the granulomas are often refractory to topical therapy. A systemic antifungal agent may be required for palliation or eradication of the infection.

*Bibliography is available at Expert Consult.*
Chapter 666  Cutaneous Fungal Infections

Bibliography

**WART (VERRUCA)
Etiology**

Human papillomaviruses (HPVs) cause a spectrum of disease from warts (verrucae vulgaris) to squamous cell carcinoma of the skin and mucous membranes, including the larynx (see Chapter 390.2). The HPVs are classified by genus, species, and type. More than 200 types are known, and the entire genomes of approximately 100 are completely sequenced. The incidence of all types of warts is highest in children and adolescents. HPV is spread by direct contact and autoinoculation; transmission within families and by fomites occurs. The clinical manifestations of infection develop 1 mo or longer after inoculation and depend on the HPV type, the size of the inoculum, the immune status of the host, and the anatomic site.

**Clinical Manifestations**

Cutaneous warts develop in 5-10% of children. **Common warts** (verruca vulgaris), caused most commonly by HPV types 2 and 4, occur most frequently on the fingers, dorsum of the hands (Fig. 667-1), paronychial areas, face, knees, and elbows. They are well-circumscribed papules with an irregular, roughened, keratotic surface. When the surface is pared away, many black dots representing thrombosed dermal capillary loops are often visible. **Periungual warts** are often painful and may spread beneath the nail plate, separating it from the nail bed (Fig. 667-2). **Plantar warts** (verruca plantaris), although similar to the common wart, are caused by HPV type 1 and are usually flush with the surface of the sole because of the constant pressure from weight bearing. When plantar warts become hyperkeratotic (Fig. 667-3), they may be painful. Similar lesions (palmar–verruca palmaris) can also occur on the palms. They are sharply demarcated, often with a ring of thick callus. The surface keratotic material must sometimes be removed before the boundaries of the wart can be appreciated. Several contiguous warts (HPV type 4) may fuse to form a large plaque, the so-called mosaic wart. Flat warts (verruca plana), caused by HPV types 3 and 10, are slightly elevated, minimally hyperkeratotic papules that usually remain <3 mm in diameter and vary in color from pink to brown. They may occur in profusion on the face, arms, dorsum of the hands, and knees. The distribution of several lesions along a line of cutaneous trauma is a helpful diagnostic feature (Fig. 667-4). Lesions may be disseminated in the beard area and on the legs by shaving and from the hairline onto the scalp by combing the hair. **Epidermodysplasia verruciformis** (EVER1, EVER2 genes), caused primarily by HPV types 5 and 8 (β-papillomaviruses, species 1), manifests as many diffuse verrucous papules. Wart types 9, 12, 14, 15, 17, 25, 36, 38, 47,
and 50 may also be involved. Inheritance is thought to be primarily autosomal recessive, but an X-linked recessive form also has been postulated. Warts progress to squamous cell carcinoma in 10% of patients with epidermodysplasia verruciformis.

Genital HPV infection occurs in sexually active adolescents, most commonly as a result of infection with HPV types 6 and 11. Condylomata acuminata (mucous membrane warts) are moist, fleshy, papillomatous lesions that occur on the perianal mucosa (Fig. 667-5), labia, vaginal introitus, and perineal raphe, and on the shaft, corona, and glans penis. Occasionally, they obstruct the urethral meatus or the vaginal introitus. Because they are located in intertriginous areas, they may become moist and friable. When untreated, condylomata proliferate and become confluent, at times forming large cauliflower-like masses. Lesions can also occur on the lips, gingivae, tongue, and conjunctivae. Genital warts in children may occur after inoculation during birth through an infected birth canal, as a consequence of sexual abuse, or from incidental spread from cutaneous warts. A significant proportion of genital warts in children contain HPV types that are usually isolated from cutaneous warts. HPV infection of the cervix is a major risk factor for development of carcinoma, particularly if the infection is caused by HPV type 16, 18, 31, 33, 35, 39, 45, 52, 59, 67, 68, or 70. Immunization against types 6, 11, 16, and 18 is now available. Laryngeal papillomatosis is caused by HPV type 16, 18, 31, 33, 35, 39, 45, 52, 59, 67, 68, or 70. Immunotherapy with intravesical candida or trichophytin antigen may also be employed especially when lesions are numerous or resistant to other tried therapies. Immunotherapy is performed in clinic and multiple treatments every month (at least 3–4) are usually required. With all types of therapy, care should be taken to protect the surrounding normal skin from irritation.

MOLLUSCUM CONTAGIOSUM

Etiology
The poxvirus that causes molluscum contagiosum is a large double-stranded DNA virus that replicates in the cytoplasm of host epithelial cells. The 3 types cannot be differentiated on the basis of clinical appearance, location of lesions, or a patient's age or sex. Type 1 virus causes most infections. The disease is acquired by direct contact with an infected person or from fomites and is spread by autoinoculation. Children age 2-6 y who are otherwise well and individuals who are immunosuppressed are affected most commonly. The incubation period is estimated to be 2 wk or longer.

Clinical Manifestations
Discrete, pearly, skin-colored, smooth, dome-shaped, papules vary in size from 1-5 mm. They typically have a central umbilication from which a plug of cheesy material can be expressed. The papules may occur anywhere on the body, but the face, eyelids, neck, axillae, and thighs are sites of predilection (Fig. 667-6). They may be found in
is diagnostic. Specific antibody against molluscum contagiosum virus is detectable in most infected individuals but is of uncertain immunologic significance. Cell-mediated immunity is thought to be important in host defense.

Treatment
Molluscum contagiosum is a self-limited disease. The average attack lasts 6-9 mo. However, lesions can persist for years, can spread to distant sites, and may be transmitted to others. Affected patients should be advised to avoid shared baths and towels until the infection is clear. Infection may spread rapidly and produce hundreds of lesions in children with atopic dermatitis or immunodeficiency. Immunotherapy with either candida or trichophyton antigen, is now the most commonly used therapy. This is repeated every 4 wk until resolution. If lesions are limited in number, then depending on the age of the patient, individual lesions can be treated with liquid nitrogen cryotherapy. For younger children, cantharidin may be applied to the lesions and covered with adhesive bandages to prevent unwanted spread of the blistering agent. A blister forms at the site of application, and the molluscum is removed with the blister. Cantharidin should not be used on the face. Cantharidin however, is now very limited or completely unavailable in the United States. Facial molluscum is more cosmetically upsetting to children and parents; imiquimod applied topically is beneficial if not excessively irritating. Molluscum is an epidermal disease and should not be overtreated such that scarring results.

Bibliography is available at Expert Consult.

clusters on the genitals or in the groin of adolescents and may be associated with other venereal diseases in sexually active individuals. Lesions commonly involve the genital area in children but are not acquired by sexual transmission in most cases. Mild surrounding erythema or an eczematous dermatitis may accompany the papules (Fig. 667-7). Lesions on patients with AIDS tend to be large and numerous, particularly on the face. Exuberant lesions may also be found in children with leukemia and other immunodeficiencies. Children with atopic dermatitis are susceptible to widespread involvement in areas of dermatitis. A pustular eruption at the site of individual molluscum lesions is seen (Fig. 667-8). It is not a secondary bacterial infection, but an immunologic reaction to the molluscum virus and it should not be treated with antibiotics. Atrophic scars are often seen after this type of reaction.

Differential Diagnosis
Differential diagnosis of molluscum contagiosum includes trichoepithelioma, basal cell carcinoma, ectopic sebaceous glands, syringoma, hidrocystoma, keratoacanthoma, and warty dyskeratoma. In individuals with AIDS, cryptococcosis may be indistinguishable clinically from molluscum contagiosum. Rarely, coccidioidomycosis, histoplasmosis, or Penicillium marneffei infection masquerades as molluscum-like lesions in an immunocompromised host.

Histology
The epidermis is hyperplastic and hypertrophied, extending into the underlying dermis and projecting above the skin surface. The central plug of material, which is composed of virus-laden cells, may be shelled out from a lesion and examined under the microscope. The rounded, cup-shaped mass of homogeneous cells, often with identifiable lobules,
Bibliography

Arthropod bites are a common affliction of children and occasionally pose a problem in diagnosis. A patient may be unaware of the source of the lesions or may deny being bitten, making interpretation of the
eruption difficult. In these cases, knowledge of the habits, life cycle, and clinical signs of the more common arthropod pests of humans may help lead to a correct diagnosis (Table 668-1).

**CLINICAL MANIFESTATIONS**

The type of reaction that occurs after an arthropod bite depends on the species of insect and the age group and reactivity of the human host. Arthropods may cause injury to a host by various mechanisms, including mechanical trauma, such as the lacerating bite of a tsetse fly; injection of host tissues, as in myiasis; contact dermatitis, as seen with repeated exposure to cockroach antigens; granulomatous reaction to retained mouthparts; transmission of systemic disease; injection of irritant cytotoxic or pharmacologically active substances, such as hyaluronidase, proteases, peptidases, and phospholipases in sting venom; and induction of anaphylaxis. Most reactions to arthropod bites depend on antibody formation to antigenic substances in saliva or venom. The type of reaction is determined primarily by the degree of previous exposure to the same or a related species of arthropod. When someone is bitten for the first time, no reaction develops. An immediate petechial reaction is occasionally seen. After repeated bites, sensitivity develops, producing a pruritic papule (Fig. 668-1) approximately 24 hr after the bite. This is the most common reaction seen in young children. With prolonged, repeated exposure, a wheal develops within minutes after a bite, followed 24 hr later by papule, vesicle, or bullae formation. By adolescence or adulthood, only a wheal may form, unaccompanied by the delayed papular reaction. Thus, adults in the same household as affected children may be unaffected. Ultimately, as a person becomes insensitive to the bite, no reaction occurs at all. This stage of nonreactivity is maintained only as long as the individual continues to be bitten regularly. Individuals in whom papular urticaria develops are in the transitional phase between development of primarily a delayed papular reaction and development of an immediate urticarial reaction.

Arthropod bites may occur as solitary, numerous, or profuse lesions, depending on the feeding habits of the perpetrator. Fleas tend to sample their host several times within a small localized area, whereas mosquitoes tend to attack a host as more randomly scattered sites. Delayed hypersensitivity reactions to insect bites, the predominant

<table>
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<tr>
<th>ARTHROPOD</th>
<th>CLINICAL FEATURES ON EXAMINATION</th>
<th>LOCATION</th>
<th>TIMING OF PRURITUS</th>
<th>CONTEXT</th>
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<td>Bed bugs</td>
<td>3-4 Bites in a line or curve</td>
<td>Uncovered areas</td>
<td>Morning</td>
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<td>Legs and buttocks</td>
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<td>Any</td>
<td>Homeless people, developing countries</td>
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<td>Vesicles, burrows, nodules, and nonspecific secondary lesions</td>
<td>Interdigital spaces, forearms, breasts, genitalia</td>
<td>Night</td>
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<td>Ticks</td>
<td>Erythema migrans or ulcer</td>
<td>Potentially anywhere</td>
<td>Asymptomatic</td>
<td>Pet owners or hikers</td>
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<td>Comet sign, a linear erythematous macular tract</td>
<td>Under clothes</td>
<td>Any time when inside habitat</td>
<td>People exposed to woodworm contaminated furniture (Pediculoides ventricosus is a woodworm parasite)</td>
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<tr>
<td>Spiders</td>
<td>Necrosis (uncommon)</td>
<td>Face and arms</td>
<td>Immediate pain, no itching</td>
<td>Rural living</td>
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*It is difficult to diagnose a bite. Diagnosis relies on an array of arguments, none of which is specific by itself; it is the association of elements that is suggestive. Any arthropod bite can be totally asymptomatic.

perivascular inflammatory infiltrate, often including a number of eosinophils. At times, however, the dermal cellular infiltrate is so dense that a lymphoma is suspected. Many young children demonstrate extensive dermal but nonerythematous, notneder edema and which responds to oral antihistamines in response to mosquito bites (“sketer” syndrome), and must be distinguished from cellulitis, which tends to be painful, tender, and red. Retained mouthparts may stimulate a foreign body type of granulomatous reaction.

**Papular urticaria** occurs principally in the 1st decade of life. It may occur at any time of the year. The most common culprits are species of fleas, mites, bedbugs, gnats, mosquitoes, chiggers, and animal lice. Individuals with papular urticaria have predominantly transitional lesions in various stages of evolution between delayed-onset papules and immediate-onset wheals. The most characteristic lesion is an edematous, red-brown papule (Fig. 668-2). An individual lesion frequently starts as a wheal that, in turn, is replaced by a papule. A given bite may incite an id reaction at distant sites of quiescent bites in the form of erythematous macules, papules, or urticarial plaques. After a season or two, the reaction progresses from a transitional to a primarily immediate hypersensitivity urticarial reaction.

One of the most commonly encountered arthropod bites is that resulting from human, cat, or dog fleas (family Pulicidae). Eggs, which are generally laid in dusty areas and cracks between floorboards, give rise to larvae that then form cocoons. The cocoon stage can persist for up to 1 yr, and the flea emerges in response to vibrations from footsteps, accounting for the assaults that frequently befall the new owners of a recently reopened dwelling. Adult dog fleas can live without a blood meal for approximately 60 days. Attacks from fleas are more likely to occur when the fleas do not have access to their usual host; cat or dog fleas are more voracious and problematic when one visits another area frequented by the pet than when the pet is encountered directly. Flea bites tend to be grouped in lines or irregular clusters on the lower extremities. Fleas are often not seen on the body of a pet. Diagnosis of flea bites is aided by examination of debris from the animal’s bedding material. The debris is collected by shaking the bedding into a plastic bag and examining the contents for fleas or their eggs, larvae, or feces.

**TREATMENT**

Treatment is directed at alleviation of pruritus by oral antihistamines and cool compresses. Potent topical corticosteroids are helpful. Topical antihistamines are potent immunologic sensitizers and have no role in the treatment of insect bite reactions. A short course of systemic steroids may be helpful if many severe reactions occur, particularly around the eyes. Insect repellents containing N,N-diethyl-3-methylbenzamide (DEET) may afford moderate protection against mosquitoes, fleas, flies, chiggers, and ticks, but are relatively ineffective against wasps, bees, and hornets. DEET must be applied to exposed skin and clothing to be effective. The most effective protection against mosquitoes, the human body louse, and other blood-feeding arthropods is use of DEET and permethrin-impregnated clothing. These measures are not effective, however, against the phlebotomine sand fly, which transmits leishmaniasis. Because of the potential for toxicity, the lowest effective DEET dose should be selected. Additional insect repellents include picaridin (flies, mosquitoes, chiggers, ticks), IR3535 (mosquitoes), oil of lemon, eucalyptus (mosquitoes), and citronella (mosquitoes). Table 668-2 lists methods to eliminate bed bugs.

**Table 668-2**

| Detection | • Look for brown insects no bigger than apple seeds on the mattress, sofa, and curtains and in darker places in the room (especially cracks in the walls, crevices in box springs, and furniture)  
| Elimination | • Look for black spots on the mattress or blood traces on the sheets  
| Prevention | • Contact a pest management company  
| | • Wash clothes at 60°C (140°F) or freeze delicate clothing, vacuum, and clean your home before the pest manager visits  
| | • Collaborate with professionals who are used to dealing with bed bug infestation to increase eradication efficacy  
| | • Carefully examine secondhand furniture to assure the absence of bed bugs before purchase so as not to contaminate your home  
| | • When sleeping in a hotel, even an upmarket establishment, lift mattresses to look for bed bugs or black spots  
| | • Do not leave luggage in dark places, near furniture, or close to your bed. Before going to bed, close suitcases and put them in the bathroom—in the bathtub or shower stall  


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**Table 668-2**

**Scabies**

Anna M. Juern and Beth A. Drolet

Scabies is caused by burrowing and release of toxic or antigenic substances by the female mite *Sarcoptes scabiei var. hominis*. The most important factor that determines spread of scabies is the extent and duration of physical contact with an affected individual. The children and sexual partner of an affected individual are most at risk. Scabies is transmitted only rarely by fomites because the isolated mite dies within 2-3 days.

**ETIOLOGY AND PATHOGENESIS**

An adult female mite measures approximately 0.4 mm in length, has 4 sets of legs, and has a hemispheric body marked by transverse corrugations, brown spines, and bristles on the dorsal surface. A male mite is approximately half her size and is similar in configuration. After impregnation on the skin surface, a gravid female exudes a keratolytic substance and burrows into the stratum corneum, often forming a shallow well within 30 min. She gradually extends this tract by...
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sites are the interdigital spaces, wrist flexors, anterior axillary folds, ankles, buttocks, umbilicus and belt line, groin, genitals in men, and areolas in women. The head, neck, palms, and soles are generally spared. Infants will often have a diffuse eczematous eruption that will involve the scalp, neck, and face. Red-brown nodules, most often located in covered areas such as the axillae, groin, and genitals, predominate in the less common variant called nodular scabies. Additional clues include facial sparing, affected family members, poor response to topical antibiotics, and transient response to topical steroids. Untreated, scabies may lead to eczematous dermatitis, impetigo, ecthyma, folliculitis, furunculosis, cellulitis, lymphangitis, and id reaction. Glomerulonephritis has developed in children from streptococcal impetiginization of scabies lesions. In some tropical areas, scabies is the predominant underlying cause of pyoderma. A latent period of approximately 1 mo follows an initial infestation. Thus, itching may be absent and lesions may be relatively inapparent in contacts who are asymptomatic carriers. On reinfestation, however, reactions to mite antigens are noted within hours.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of scabies can often be made clinically but is confirmed by microscopic identification of mites (Fig. 668-5A), ova, and scybala (Fig. 668-5B) in epithelial debris. Scrapings most often test positive when obtained from burrows or fresh papules. A reliable method is application of a drop of mineral oil on the selected lesion, scraping of it with a No. 15 blade, and transferring the oil and scrapings to a glass slide.

The differential diagnosis depends on the types of lesions present. Burrows are virtually pathognomonic for human scabies. Papulovesicular lesions are confused with papular urticaria, canine scabies, chickenpox, viral exanthems, drug eruptions, dermatitis herpetiformis, and folliculitis. Eczematous lesions may mimic atopic dermatitis and seborrheic dermatitis, and the less common bullous disorders of childhood may be suspected in infants with predominantly bullous lesions. Nodular scabies is frequently misdiagnosed as urticaria pigmentosa and Langerhans cell histiocytosis. The histopathologic appearance of nodular scabies, consisting of a deep, dense, perivascular infiltrate of lymphocytes, histiocytes, plasma cells, and atypical mononuclear cells, may mimic malignant lymphoid neoplasms.
The infestation is often accompanied by generalized lymphadenopathy.

In patients who have severe systemic illness (leukemia, diabetes), the rash is pruritic and has a predilection for the arms, chest, and abdomen, the usual sites of contact with dogs. Onset is sudden and usually follows exposure by 1-10 days, possibly resulting from development of a hypersensitivity reaction to mite antigens. Recovery of mites or ova from scrapings of human skin is rare. The disease is self-limited because humans are not a suitable host. Bathing and changing clothes are generally sufficient. Removal or treatment of the infested animal is necessary. Symptomatic therapy for itching is helpful. In rare cases in which mites are demonstrated in scrapings from an affected child, they can be eradicated by the same measures applicable to human scabies.

OTHER TYPES OF SCABIES

Other mites that occasionally bite humans include the chigger or harvest mite (Eutrombicula alfredredoguis), which prefers to live on grass, shrubs, vines, and stems of grain. Larvae have hooked mouthparts, which allow the chigger to attach to the skin, but not to burrow, to leaves, branches, stems, and roots of plants. Chiggers prefer to feed at dawn and dusk and are most active under conditions of high humidity. They can affect not only humans but also domestic animals. Human reactions to chigger bites are usually delayed. The bite, which is usually multiple, is characterized by development of a vesicle, redness, and pruritus, which can progress to a large, inflamed, red, and edematous papule. Pruritus, if present, usually begins 1-2 days after feeding and can persist for 1-2 wk. Infestation can cause significant pruritus and discomfort.

Scabies ova and scybala.

**Figure 668-5** A, Human scabies mite obtained from scraping. B, Scabies ova and scybala.

**TREATMENT**

The treatment of choice for scabies is permethrin 5% cream (Elimite) applied to the entire body from the neck down, with particular attention to intensely involved areas, which is also standard therapy. Scabies is frequently found above the neck in infants (younger than 2 yr old), necessitating treatment of the scalp. The medication is left on the skin for 8-12 hr and should be reapplied in 1 wk for another 8-12 hr period. Additional therapies may include lindane 1% lotion or cream, sulfur ointment 5-10%, and crotamiton 10% lotion or cream. For severe infestations and in immunocompromised patients oral ivermectin 200 µg/kg per dose given orally for 2 doses, 2 wk apart can be used (off-label use). Single dose ivermectin (200 µg/kg) has also been effective in immunocompetent patients with improvement (cure) noted in 60% at 2 wk and 89% at 4 wk after treatment.

Transmission of mites is unlikely more than 24 hr after treatment. Pruritus, which is a result of hypersensitivity to mite antigens, may persist for a number of days to weeks, and may be alleviated by a topical corticosteroid preparation. If pruritus persists for >2 wk after treatment and new lesions are occurring, the patient should be reexamined for mites. Nodules are extremely resistant to treatment and may take several months to resolve. The entire family should be treated, as should caretakers of the infested child. Clothing, bed linens, and towels should be washed in hot water and dried using high heat. Clothing or other items (e.g., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 wk, as the mite will die when separated from the human host.

**NORWEGIAN SCABIES**

The Norwegian variant of human scabies is highly contagious and occurs mainly in individuals who are cognitively and physically debilitated, particularly those who are institutionalized and those with Down syndrome; in patients with poor cutaneous sensation (leprosy, spina bifida); in patients who have severe systemic illness (leukemia, diabetes); and in immunosuppressed patients (HIV infection). Affected individuals are infested by myriad mites that inhabit the crusts and exfoliating scales of the skin and scalp. The nails may become thickened and dystrophic. The subungual debris is densely populated by mites. The infestation is often accompanied by generalized lymphadenopathy and eosinophilia. There is massive orthokeratosis and parakeratosis with numerous interspersed mites, psoriasiform epidermal hyperplasia, foci of spongiosis, and neutrophilic abscesses. Norwegian scabies is thought to represent a deficient host immune response to the organism. Management is difficult, requiring scrupulous isolation measures, removal of the thick scales, and repeated but careful applications of permethrin 5% cream. Ivermectin (200-250 µg/kg) has been used successfully as single-dose therapy in refractory cases, particularly in HIV-infected patients. A second dose may be needed a week later. The FDA has not approved this agent for treatment of scabies.

**CANINE SCABIES**

Canine scabies is caused by *S. scabiei* var. *canis*, the dog mite that is associated with mange. The eruption in humans, which is most frequently acquired by cuddling an infested puppy, consists of tiny papules, vesicles, wheals, and excoriated eczematous plaques. Burrows are not present because the mite infrequently inhabits human stratum corneum. The rash is pruritic and has a predilection for the arms, chest, and abdomen, the usual sites of contact with dogs. Onset is sudden and usually follows exposure by 1-10 days, possibly resulting from development of a hypersensitivity reaction to mite antigens. Recovery of mites or ova from scrapings of human skin is rare. The disease is self-limited because humans are not a suitable host. Bathing and changing clothes are generally sufficient. Removal or treatment of the infested animal is necessary. Symptomatic therapy for itching is helpful. In rare cases in which mites are demonstrated in scrapings from an affected child, they can be eradicated by the same measures applicable to human scabies.

**OTHER TYPES OF SCABIES**

Other types of pediculosis is pruritus. But develop as an individual becomes sensitized. The hallmark of all types of pediculosis is pruritus. Which is a result of hypersensitivity to mite antigens, may persist for a number of days to weeks, and may be alleviated by a topical corticosteroid preparation. If pruritus persists for >2 wk after treatment and new lesions are occurring, the patient should be reexamined for mites. Nodules are extremely resistant to treatment and may take several months to resolve. The entire family should be treated, as should caretakers of the infested child. Clothing, bed linens, and towels should be washed in hot water and dried using high heat. Clothing or other items (e.g., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 wk, as the mite will die when separated from the human host.

Three types of lice are obligate parasites of the human host: body or clothing lice (*Pediculus humanus corporis*), head lice (*Pediculus humanus capitis*), and pubic or crab lice (*Phthirus pubis*). Only the body louse serves as a vector of human disease (typhus, trench fever, relapsing fever). Body and head lice have similar physical characteristics. They are approximately 2-4 mm in length. Body lice are only 1-2 mm in length and are greater in width than length, giving them a crab-like appearance. Female lice live for approximately 1 mo and deposit 3-10 eggs daily on the human host. Body lice, however, generally lay eggs in or near the seams of clothing. The ova or nits are glued to hairs or fibers of clothing but not directly on the body. Ova hatch in 1-2 wk and require another week to mature. Once the eggs hatch, the nits remain attached to the hair as empty sacs of chitin. Freshly hatched larvae die unless a meal is obtained within 24 hr and every few days thereafter. Both nymphs and adult lice feed on human blood, injecting their salivary juices into the host and depositing their fecal matter on the skin. Symptoms of infestation do not appear immediately but develop as an individual becomes sensitized. The hallmark of all types of pediculosis is pruritus.

**Bibliography is available at Expert Consult.**
Bibliography
Goddard J, deShazo R: Bed bugs (Cimex lectularius) and clinical consequences of their bites, JAMA 301:1358–1366, 2009.
Pediculosis corporis is rare in children except under conditions of poor hygiene, especially in colder climates when the opportunity to change clothes on a regular basis is lacking. The parasite is transmitted mainly on contaminated clothing or bedding. The primary lesion is a small, intensely pruritic, red macule or papule with a central hemorrhagic punctum, located on the shoulders, trunk, or buttocks. Additional lesions include excoriations, wheals, and eczematous, secondarily infected plaques. Massive infestation may be associated with constitutional symptoms of fever, malaise, and headache. Chronic infestation may lead to “vagabond’s skin,” which manifests as lichenified, scaling, hyperpigmented plaques, most commonly on the trunk. Lice are found on the skin only transiently when they are feeding. At other times, they inhabit the seams of clothing. Nits are attached firmly to fibers in the cloth and may remain viable for up to 1 mo. Nits hatch when they encounter warmth from the host’s body when the clothes are worn again. Therapy consists of improved hygiene and hot water laundering of all infested clothing and bedding. A uniform temperature of 65°C (149°F), wet or dry, for 15-30 min kills all eggs and lice. Alternatively, eggs hatch and nymphs starve if clothing is stored for 2 wk at 23.9-29.4°C (75-85°F).

Pediculosis capitis is an intensely pruritic infestation of lice in the scalp hair. It is the most common form of lice to affect children, in particular those between the ages of 3 and 12 yr. Fomites and head-to-head contact are important modes of transmission. In summer months in many areas of the United States and in the tropics at all times of the year, shared combs, brushes, or towels have a more important role in louse transmission. Translucent 0.5 mm eggs are laid near the proximal portion of the hair shaft and become adherent to 1 side of the shaft (Fig. 668-6). A nit cannot be moved along or knocked off the hair shaft with the fingers. Secondary pyoderma, after trauma from scratching, may result in matting together of the hair and cervical and occipital lymphadenopathy. Hair loss does not result from pediculosis but may accompany the secondary pyoderma. Head lice are a major cause of numerous pyoderma of the scalp, particularly in tropical environments. Lice are not always visible, but nits are detectable on the hairs, most commonly in the occipital region and above the ears, rarely on beard or pubic hair. Dermatitis may also be noted on the neck and pinnae. An id reaction, consisting of erythematous patches and plaques, may develop, particularly on the trunk. Head lice rarely infest African-Americans and this is possibly related to the diameter, shape or twisted nature of their hair shafts (which makes grasping of the shaft more difficult for the louse).

Because of resistance of head lice to pyrethroids, malathion 0.5% in isopropanol is the treatment of choice for head lice and should be applied to dry hair until hair and scalp are wet, and left on for 12 hr. A second application 7-9 days after initial treatment may be necessary. This product is flammable, so care should be taken to avoid open flames. Malathion, like lindane shampoo, is not indicated for use in neonates and infants. Additional approved therapies include spinosad (if <4 yr old), benzyl alcohol lotion (if >6 mo), and ivermectin for difficult-to-treat head lice (Table 668-3). All household members should be treated at the same time. Nits can be removed with a fine-toothed comb after application of a damp towel to the scalp for 30 min. Clothing and bed linens should be laundered in very hot water or dry-cleaned; brushes and combs should be discarded or coated with a pediculicide for 15 min and then thoroughly cleaned in boiling water. Children may return to school after the initial treatment.

Pediculosis pubis is transmitted by skin-to-skin or sexual contact with an infested individual; the chance of acquiring the lice with 1 sexual exposure is 95%. The infestation is usually encountered in adolescents, although small children may occasionally acquire pubic lice on the eyelashes. Patients experience moderate to severe pruritus and may develop a secondary pyoderma from scratching. Excoriations tend to be shallower, and the incidence of secondary infection is lower than in pediculosis corporis. Maculae ceruleae are steel-gray spots, usually <1 cm in diameter, which may appear in the pubic area and on the chest, abdomen, and thighs. Oval translucent nits, which are firmly attached to the hair shafts, may be visible to the naked eye or may be readily identified by a hand lens or by microscopic examination (see Fig. 668-6). Grittiness, as a result of adherent nits, may sometimes be detected when the fingers are run through infested hair. Adult lice are difficult to detect than head or body lice because of their lower level of activity and smaller, translucent bodies. Because pubic lice occasionally may wander or may be transferred to other sites on fomites, terminal hair on the trunk, thighs, axillary region, beard area, and eyelashes should be examined for nits. The coexistence of other venereal diseases should be considered. Treatment with a 10-min application of a pyrethrin preparation is usually effective. Retreatment may be required in 7-10 days. The shampoo form of lindane, which requires a 10 min application time, is an alternative choice, but lindane cream and lotion are no longer recommended for treatment of pubic lice. Infestation of eyelashes is eradicated by petrolatum applied 3-5 times per 24 hr for 8-10 days. Clothing, towels, and bed linens may be contaminated with nit-bearing hairs and should be thoroughly laundered or dry-cleaned.

Bibliography is available at Expert Consult.

668.4 Seabather’s Eruption
Anna M. Juern and Beth A. Drolet

Seabather’s eruption is a severely pruritic dermatosis of inflammatory papules that develops within ≈12 hr of bathing in saltwater, primarily on body sites that were covered by a bathing suit. The eruption has been described primarily in connection with bathing in the waters of Florida and the Caribbean. Lesions, which may include pustules, vesicles, and urticarial plaques, are more numerous in individuals who keep their bathing suits on for an extended period after leaving the water. The eruption may be accompanied by systemic symptoms of fatigue, malaise, fever, chills, nausea, and headache; in 1 large series, ≈40% of children younger than 16 yr of age had fever. Duration of the pruritus and skin eruption is 1-2 wk. Lesions consist of a superficial and deep perivascular and interstitial infiltrate of lymphocytes, eosinophils, and neutrophils. The eruption appears to be due to an allergic hypersensitivity reaction to venom from larvae of the thimble jellyfish (Linuche unguiculata). Treatment is largely symptomatic. Potent topical corticosteroids have been shown to provide relief to some patients.

Figure 668-6 Intact nits on human hairs.
**Bibliography**


<table>
<thead>
<tr>
<th>DRUG</th>
<th>RESISTANCE</th>
<th>LOWER AGE OR WEIGHT LIMIT</th>
<th>DOSAGE AND ADMINISTRATION</th>
<th>COST/SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin 0.5% lotion–Sklice</td>
<td>No³</td>
<td>6 months</td>
<td>Apply to dry hair and scalp for 10 min, then rinse</td>
<td>$257.88/4 oz</td>
</tr>
<tr>
<td>(Sanofi Pasteur)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivermectin tablets–Stromectol</td>
<td>No</td>
<td>15 kg</td>
<td>200-400 µg/kg PO once; repeat 7-10 days later</td>
<td>9.97³</td>
</tr>
<tr>
<td>(Merck)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinosad 0.9% suspension–Natroba</td>
<td>No³</td>
<td>4 yr</td>
<td>Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary</td>
<td>219.00/4 oz</td>
</tr>
<tr>
<td>(ParaPro)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl alcohol 5% lotion–Ulesfia</td>
<td>No</td>
<td>6 months</td>
<td>Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary</td>
<td>52.62/8 oz</td>
</tr>
<tr>
<td>(Shionogi)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrethrins with piperonyl butoxide</td>
<td>Yes</td>
<td>2 yr</td>
<td>Apply to dry hair for 10 min, then shampoo; repeat 7-10 days later</td>
<td>12.49/8 oz</td>
</tr>
<tr>
<td>shampoo³–Generic Rid (Bayer)</td>
<td></td>
<td></td>
<td></td>
<td>19.99/8 oz²</td>
</tr>
<tr>
<td>Permethrin 1% creme rinse²–Generic Nix</td>
<td>Yes</td>
<td>2 months</td>
<td>Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later</td>
<td>18.49/4 oz</td>
</tr>
<tr>
<td>(Insight)</td>
<td></td>
<td></td>
<td></td>
<td>19.99/4 oz²</td>
</tr>
<tr>
<td>Malathion 0.5% lotion–Generic Ovide</td>
<td>Not in U.S.</td>
<td>6 yr</td>
<td>Apply to dry hair for 8-12 hr,¹ then shampoo; repeat 7-9 days later if necessary</td>
<td>152.67/2 oz</td>
</tr>
<tr>
<td>(Taro)</td>
<td></td>
<td></td>
<td></td>
<td>160.46/2 oz</td>
</tr>
</tbody>
</table>

¹Wholesale acquisition cost (WAC). Source: PricePointRx. Reprinted with permission by FDB, Inc. All rights reserved. Copyright 2012. www.firstdatabank.com/support/drug-pricing-policy.aspx. Actual retail prices may be higher. Amount needed may vary.
²Product new to market: currently no reports of resistance.
³Not FDA-approved for treatment of head lice. Stromectol is available in 3 mg tablets.
⁴Cost of 1 dose for a 30 kg child at the lowest dosage.
⁵Available without a prescription.
⁶Products that contain benzyl alcohol as their vehicle may be more effective.
⁷Cost according to drugstore.com.
¹⁸One or two 20 min applications have also been effective (Meinking TL, Vicaria M, Eyerdam DH, et al: Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix creme rinse (1% permethrin) for the treatment of head lice, Pediatr Dermatol 21:670-674, 2004.)

ACNE VULGARIS

Acne, particularly the comedonal form, occurs in 80% of adolescents.

Pathogenesis

Lesions of acne vulgaris develop in sebaceous follicles, which consist of large, multilobular sebaceous glands that drain their products into the follicular canals. The initial lesion of acne is a microcomedone, which progresses to a comedone. A comedone is a dilated epithelium-lined follicular sac filled with lamellated keratinous material, lipid, and bacteria. An open comedone, known as a blackhead, has a patulous pilosebaceous orifice that permits visualization of the plug. An open comedone becomes inflammatory less commonly than does a closed comedone or whitehead, which has only a pinpoint opening. An inflammatory papule or nodule develops from a comedone that has ruptured and extruded its follicular contents into the subjacent dermis, inducing a neutrophilic inflammatory response. If the inflammatory reaction is close to the surface, a papule or pustule develops. If the inflammatory infiltrate develops deeper in the dermis, a nodule forms. Suppuration and an occasional giant cell reaction to the keratin and hair are the cause of nodulocystic lesions. These are not true cysts but liquefied masses of inflammatory debris.

The primary pathogenetic alterations in acne are (1) abnormal keratinization of the follicular epithelium, resulting in impaction of keratinized cells within the follicular lumen; (2) increased sebaceous gland production of sebum; (3) proliferation of Propionibacterium acnes within the follicle; and (4) inflammation. Comedonal acne (Fig. 669-1), particularly of the central face, is frequently the first sign of pubertal maturation. At puberty, the sebaceous gland enlarges and sebum production increases in response to the increased activities of androgens of primarily adrenal origin. Most patients with acne do not have endocrine abnormalities. Hyperresponsiveness of the sebocyte to androgens is likely involved in determining the severity of acne in a given individual. Sebocytes and follicular keratinocytes contain 5α-reductase and 3β- and 17β-hydroxyl-steroid dehydrogenase, which are capable of metabolizing androgens. A significant number of women with acne (25-50%), particularly those with

Figure 669-1 Primarily comedonal acne in a 7 yr old girl.
Lesions may also involve the chest, upper back, and deltoid areas. A predominance of lesions on the forehead, particularly closed comedones, is often attributable to prolonged use of greasy hair preparations (pomade acne) (Fig. 669-4). Marked involvement on the trunk is most often seen in males. Lesions often heal with temporary postinflammatory erythema and hyperpigmentation. Pitted, atrophic, or hypertrophic scars may be interspersed, depending on the severity, depth, and chronicity of the process. Diagnosis of acne is rarely difficult, although flat warts, folliculitis, and other types of acne (drug induced: glucocorticoid agents, anabolic steroids, gold, dactinomycin, isoniazid, lithium, phenytoin, progestins) may be confused with acne vulgaris. The differential diagnosis includes sarcoidosis, angiofibromas, keratosis pilaris, chloracne, rosacea, and fibrofolliculomas.

**Clinical Manifestations**

Acne vulgaris is characterized by 4 basic types of lesions: open and closed comedones, papules, pustules (Fig. 669-2), and nodulocystic lesions (Fig. 669-3 and Table 669-1). One or more types of lesions may predominate. In its mildest form, which is often seen early in adolescence, lesions are limited to comedones on the central area of the face.

<table>
<thead>
<tr>
<th>Table 669-1</th>
<th>Classification of Acne</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEVERITY</strong></td>
<td><strong>DESCRIPTION</strong></td>
</tr>
<tr>
<td>Mild</td>
<td>Comedones (noninflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally &lt;10).</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate numbers of papules and pustules (10-40) and comedones (10-40) are present. Mild disease of the trunk may also be present.</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>Numerous papules and pustules are present (40-100), usually with many comedones (40-100) and occasional larger, deeper nodular inflamed lesions (up to 5). Widespread affected areas usually involve the face, chest, and back.</td>
</tr>
<tr>
<td>Severe</td>
<td>Nodulocystic acne and acne conglobata, with many large, painful nodular or pustular lesions, are present, along with many smaller papules, pustules, and comedones.</td>
</tr>
</tbody>
</table>

The pediatrician must be aware of the frequently poor correlation between acne severity and psychosocial impact, particularly in adolescents. As adolescents become preoccupied with their appearance, offering treatment even to the younger whose acne is mild may enhance self-image.

**Diet**

Little evidence shows that ingestion of particular foods can trigger acne flares. When a patient is convinced that certain dietary items exacerbate acne, it is prudent for the patient to omit those foods.

**Climate**

Climate appears to influence acne, in that improvement frequently occurs in summer and flares are more common in winter. Remission in summer may relate, in part, to the relative absence of stress. Emotional tension and fatigue seem to exacerbate acne in many individuals;

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**Table 669-2 Typical Treatment Regimens for Acne**

<table>
<thead>
<tr>
<th>COMEDONAL ACNE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical retinoid or azelaic acid or salicylic acid</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MILD PAPULOPUSTULAR ACNE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical retinoid plus benzoyl peroxide or benzoyl peroxide/topical antibiotic or benzoyl peroxide/oral antibiotic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEVERE PAPULOPUSTULAR OR NODULAR ACNE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical retinoid plus benzoyl peroxide and oral antibiotic or isotretinoin 1 mg/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 669-5 Acne treatment algorithm.** BPO, benzoyl peroxide. (From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al: New insights into the management of acne: an update from the global alliance to improve outcomes in acne, J Am Acad Dermatol 60:S1–S50, 2009.)

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The mechanism is unclear but has been proposed to relate to an increased adrenocortical response.

**Cleansing**

Cleansing with soap and water removes surface lipid and renders the skin less oily in appearance, but no evidence shows that surface lipid has a role in generating acne lesions. Only superficial drying and peeling are achieved by cleansing, and almost any mild soap or astrin- gent is adequate. Repetitive cleansing can be harmful because it irritates and chaps the skin. Cleansing agents that contain abrasives and keratolytic agents, such as sulfur, resorcinol, and salicylic acid, may temporarily remove sebum from the skin surface. They exert a mild drying and peeling effect and suppress lesions to a limited degree. They do not prevent microcomedones from forming. No evidence shows that preparations containing alcohol or hexachlorophene decrease acne because surface bacteria are not involved in the pathogenesis. Greasy cosmetic and hair preparations must be discontinued because they exacerbate preexisting acne and cause further plugging of follicular pores. Manipulation and squeezing of facial lesions only ruptures intact lesions and provokes a localized inflammatory reaction.

**Topical Therapy**

All topical preparations must be used for 6-8 wk before their effectiveness can be assessed. Retinoids may be used alone for mild acne, but combination therapy is frequently more effective. A popular and effective combination is use of benzoyl peroxide gel in the morning and a retinoid at night.

**Retinoids.** A topical retinoid should be the primary treatment for acne vulgaris. Topical retinoids have multiple actions, including inhibition of the formation and number of microcomedones, reduction of mature comedones, reduction of inflammatory lesions, and production of normal desquamation of the follicular epithelium. Retinoids should be applied daily to all the affected areas. The main side effects of retinoids are irritation and dryness. Not all patients initially respond.
tolerate daily use of a retinoid. It is prudent to begin therapy every other or every 3rd day and slowly increase the frequency of application as tolerated. Tretinoin, adapalene, and tazarotene (Table 669-3) are the available retinoids. They vary in strength and efficacy, although adapalene tends to be less irritating and tazarotene is more irritating but may be more effective.

**Benzoyl Peroxide.** Benzoyl peroxide is primarily an antimicrobial agent. It has an advantage over topical antibiotics in that it does not enhance antimicrobial resistance. It is available in multiple formulations and concentrations. The gel formulations are preferred, owing to better stability and more consistent release of the active ingredient. Washes and cleansers are useful for covering large surface areas such as the chest and back. As with retinoids, the main side effects are irritation and drying. Benzoyl peroxide can also bleach clothing.

**Topical Antibiotics.** Topical antibiotics are indicated for the treatment of inflammatory acne. Clindamycin is the most commonly used. It is not as effective as oral antibiotics. It should not be used as monotherapy because it does not inhibit microcomedone formation and it has the potential to induce antimicrobial resistance. Irritation and dryness are generally less than with retinoids or benzoyl peroxide. Topical antibiotics are best used as combination products. The most common is benzoyl peroxide/clindamycin. A combination tretinoin/clindamycin product may also be used.

### Table 669-3 Medications for the Treatment of Acne

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>SIDE EFFECT(S)</th>
<th>OTHER CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOPICAL AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Retinoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Applied once nightly; strengths of 0.025-0.1% available**</td>
<td>Irritation (redness and scaling)</td>
<td>Generics available</td>
</tr>
<tr>
<td>Adapalene</td>
<td>Applied once daily, at night or in the morning; 0.01% and 0.3%**</td>
<td>Minimal irritation</td>
<td>0.1% generic available</td>
</tr>
<tr>
<td>Tazarotene*</td>
<td>Applied once nightly; 0.05% and 0.1%**</td>
<td>Irritation</td>
<td>Limited data suggest tazarotene more effective than alternatives</td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoyl peroxide, alone or with zinc, 2.5-10%</td>
<td>Applied once or twice daily</td>
<td>Benzoyl peroxide can bleach clothing and bedding</td>
<td>Available over the counter; 2.5-5% concentrations as effective as and less drying than 10% concentration</td>
</tr>
<tr>
<td>Clindamycin, erythromycin†</td>
<td>Applied once or twice daily</td>
<td>Propensity to resistance</td>
<td>Most effective for inflammatory lesions (rather than comedones); resistance a concern when used alone</td>
</tr>
<tr>
<td>Combination benzoyl peroxide and clindamycin or erythromycin</td>
<td>Applied once or twice daily</td>
<td></td>
<td>Combination more effective than topical antibiotics alone; limits development of resistance; use of individual products in combination less expensive and appears similarly effective</td>
</tr>
<tr>
<td>Combination tretinoin and clindamycin</td>
<td>Applied once or twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Topical Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelaic acid, sodium sulfacetamide-sulfur, salicylic acid†</td>
<td>Applied once or twice daily</td>
<td>Well tolerated</td>
<td>Good adjunctive or alternative treatments</td>
</tr>
<tr>
<td><strong>ORAL ANTIMICROBIALS</strong>‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline§</td>
<td>250-500 mg once or twice daily</td>
<td>Gastrointestinal upset, pseudomotor cerebri, pill esophagitis, gastrointestinal upset</td>
<td>Inexpensive; dosing limited by need to take on empty stomach; 20 mg dose antiinflammatory only; limited data on efficacy</td>
</tr>
<tr>
<td>Doxycycline§</td>
<td>50-100 mg once or twice daily</td>
<td>Phototoxicity, pseudomotor cerebri, pill esophagitis, gastrointestinal upset</td>
<td></td>
</tr>
<tr>
<td>Minocycline§</td>
<td>50-100 mg once or twice daily</td>
<td>Hyperpigmentation of teeth, oral mucosa, and skin; lupus-like reactions with long-term treatment, pseudomotor cerebri, DRESS</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>One dose (160 mg trimethoprim, 800 mg sulfamethoxazole) twice daily</td>
<td>Toxic epidermal necrolysis and allergic eruptions</td>
<td>Trimethoprim may be used alone in 300 mg dose twice daily; limited data available</td>
</tr>
<tr>
<td>Erythromycin†</td>
<td>250-500 mg twice daily</td>
<td>Gastrointestinal upset</td>
<td>Resistance problematic; consensus is that efficacy is limited</td>
</tr>
<tr>
<td><strong>HORMONAL AGENTS</strong>§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone§</td>
<td>50-200 mg in divided doses</td>
<td>Menstrual irregularities, breast tenderness</td>
<td>Higher doses more effective but cause more side effects; best given in combination with oral contraceptives</td>
</tr>
<tr>
<td>Estrogen-containing oral contraceptives</td>
<td>Daily</td>
<td>Potential side effects include thromboembolism</td>
<td></td>
</tr>
</tbody>
</table>

**Continued**
Azelaic Acid. Azelaic acid (20% cream) has mild antimicrobial and keratolytic properties. It can also help expedite resolution of postinflammatory hyperpigmentation.

Systemic Therapy
Antibiotics, especially tetracycline and its derivatives (see Table 669-3), are indicated for treatment of patients whose acne has not responded to topical medications, who have moderate to severe inflammatory papulopustular and nodulocystic acne, and who have a propensity for scarring. Tetracycline and its derivatives act by reducing the growth and metabolism of P. acnes. They also have antiinflammatory properties. For most adolescent patients, therapy may be initiated twice daily, for at least 6-8 wk, followed by a gradual decrease to the minimal effective dose. The drugs should always be administered in combination with a topical retinoid and topical benzoyl peroxide, but not topical antibiotics. Tetracycline absorption is inhibited by food, milk, iron supplements, and calcium-magnesium salts. It should be taken on an empty stomach 1 hr before or 2 hr after meals. Minocycline and doxycycline may be taken with food. Side effects of tetracycline and derivatives are rare. Side effects of tetracycline include vaginal candidiasis, particularly in those who take tetracycline concurrently with oral contraceptives; gastrointestinal irritation; photosensitive reactions, including erythema, urticaria, and pruritus; and photosensitization of the tetracycline derivatives and is also more likely to cause photodermatitis. Rarely, minocycline causes dizziness, intracranial hypertension, bluish discoloration of the skin and mucous membranes, hepatitis, a lupus-like syndrome, and drug reaction with eosinophilia and systemic symptoms. A possible complication of prolonged systemic antibiotic use is proliferation of Gram-negative organisms, particularly Enterobacter, Klebsiella, Escherichia coli, and Pseudomonas aeruginosa, producing severe, refractory folliculitis.

Women who have acne and hormonal abnormalities, whose acne is unresponsive to antibiotic therapy, or who are not candidates for isotretinoin therapy should be considered for a trial of hormonal therapy. Combined oral contraceptive pills are the primary form of hormonal therapy. Spironolactone has also shown effectiveness.

Isotretinoin (13-cis-retinoic acid; Accutane) is indicated for severe nodulocystic acne and moderate to severe acne that has not responded to conventional therapy. The recommended dosage is 0.5-1.0 mg/kg/day. A standard course in the United States lasts 16-20 wk. At the end of 1 course of isotretinoin, 70-80% of patients are cured, 10-20% need conventional topical and/or oral medications to maintain adequate control, and 10-20% have relapses and need an additional course of isotretinoin. Dosages <0.5 mg/kg/day, or a cumulative dose of <120 mg/kg, are associated with a significantly higher rate of treatment failure and relapse. If the disease process is not in remission 2 mo after the first course of isotretinoin, a second course should be considered. Isotretinoin reduces size and secretion of sebaceous glands, normalizes follicular keratinization, prevents new microcomedone formation, decreases the population of P. acnes, and exerts an antiinflammatory effect.

Isotretinoin use has many side effects. It is highly teratogenic and is absolutely contraindicated in pregnancy. Pregnancy should be avoided for 6 wk after discontinuation of therapy. Two forms of birth control are required, as are monthly pregnancy tests. Concerns over cases of pregnancy despite warnings have prompted a manufacturer registration program, iPLEDGE (www.ipledgeprogram.com), which requires prescriber isotretinoin. Many patients also experience chilblains, xerosis, periodontal epistaxis, and blepharoconjunctivitis. Increased serum triglyceride and cholesterol levels are also common. It is important to rule out

<table>
<thead>
<tr>
<th>Table 669-3</th>
<th>Medications for the Treatment of Acne—cont’d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>DOSE</strong></td>
</tr>
<tr>
<td>Isotretinoin (Accutane)</td>
<td>0.5-1.0 mg/kg/day in divided doses</td>
</tr>
<tr>
<td>Absorica (isotretinoin agent)</td>
<td>0.5-1 mg/kg/day bid</td>
</tr>
</tbody>
</table>

*Tazarotene is in pregnancy category X: contraindicated in pregnancy.
†Clindamycin, erythromycin, and azelaic acid are in pregnancy category B: no evidence of risk in humans.
‡Oral antibiotics are indicated for moderate to severe disease; for the treatment of acne on the chest, back, or shoulders; and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.
§This drug is in pregnancy category D: positive evidence of risk in humans.
¶Hormonal agents are for use in women only.
**As cream or gel. DRESS, drug rash with eosinophilia and systemic symptoms.

Acne

Follows the initiation of steroid therapy by approximately 2 wk. The lesions are small, erythematous papules or pustules that may erupt in profusion and are all in the same stage of development. Comedones may occur subsequently, but nodulocystic lesions and scarring are rare. Pruritus is occasional. Although steroid acne is relatively refractory if the medication is continued, the eruption may respond to use of tretinoin and a benzoyl peroxide gel.

Other drugs that can induce acneiform lesions in susceptible individuals include isoniazid, phenytoin, phenobarbital, trimethadione, lithium carbonate, androgens (anabolic steroids), and vitamin B12.

### Surgical Therapy

Intralesional injection of low-dose (3-5 mg/mL) mid-potency glucocorticoids (e.g., triamcinolone) with a 30-gauge needle on a tuberculin syringe may hasten the healing of individual, painful nodulocystic lesions. Dermabrasion or laser peel to minimize scarring should be considered only after the active process is quiescent. Figure 669-6 describes the management of scarring. The role of pulsed-dye laser in the treatment of inflammatory acne is controversial and inconclusive.

### Non-ablative lasers for mild disease; ablative and fractional lasers for moderate scarring

**Figure 669-6** Treatment options for acne scars. CO₂, carbon dioxide; FU, fluorouracil; TCA, trichloroacetic acid. (From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al: New insights into the management of acne: an update from the global alliance to improve outcomes in acne, J Am Acad Dermatol 60:S1–S50, 2009.)

<table>
<thead>
<tr>
<th>Punch excision (deep bases)</th>
<th>Combined therapy</th>
<th>Shallow ≤3 mm diameter-laser skin resurfacing</th>
<th>Intraliesional corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation and grafting</td>
<td>Micrograft and subcision +</td>
<td>&gt;3 mm diameter-laser skin resurfacing ≥ punch elevation</td>
<td>Intraliesional 5-FU</td>
</tr>
<tr>
<td>Laser resurfacing/dermabrasion (many scars close together)</td>
<td>± filler</td>
<td></td>
<td>Intraliesional bleomycin</td>
</tr>
<tr>
<td>Spot TCA peel</td>
<td>Resurfacing microdermabrasion</td>
<td>Deep ≤3 mm diameter-punch excision</td>
<td>Compression</td>
</tr>
<tr>
<td></td>
<td>Deep-spot TCA peel</td>
<td>&gt;3 mm diameter-punch excision or punch elevation</td>
<td>Imiquimod after intraliesional excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fractional thermolysis (deep or shallow)</td>
<td>Cryotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermabrasion</td>
<td>Pulsed-dye laser</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO₂ laser resurfacing</td>
<td>Excision + electrotherapy</td>
</tr>
</tbody>
</table>

**Figure 669-7** Monomorphous papular eruption of steroid acne.
HALOGEN ACNE
Administration of medications containing iodides or bromides or, rarely, ingestion of massive amounts of vitamin–mineral preparations or iodine-containing “health foods” such as kelp may induce halogen acne. The lesions are often very inflammatory. Discontinuation of the provocative agent and appropriate topical preparations usually achieve reasonable therapeutic results.

CHLORACNE
Chloracne is a result of external contact with, inhalation of, or ingestion of halogenated aromatic hydrocarbons, including polyhalogenated biphenyls, polyhalogenated naphthalenes, and dioxins. Lesions are primarily comedonal. Inflammatory lesions are infrequent but may include papules, pustules, nodules, and cysts. Healing occurs with atrophic or hypertrophic scarring. The face, postauricular regions, neck, axillae, genitals, and chest are most commonly involved. The nose is often spared. In cases of severe exposure, associated findings may include hepatitis, production of porphyrins, bulla formation on sun-exposed skin, hyperpigmentation, hypertrichosis, and palmar and plantar hyperhidrosis. Topical or oral retinoids may be effective; benzoyl peroxide and antibiotics are generally ineffective.

NEONATAL ACNE
Approximately 20% of normal neonates demonstrate acne in the 1st mo of life. Small inflammatory papules and pustules predominate on the cheeks and forehead (Fig. 669-8); comedones are absent. The cause of neonatal acne is unknown but it has been theorized that it may be an inflammatory reaction to Pityrosporum species rather than true acne; therefore, the term neonatal cephalic pustulosis has been proposed. Other theories include placental transfer of maternal endogenous, hyperactive neonatal adrenal glands, and a hypersensitive neonatal end-organ response to androgenic hormones. The eruption involutes spontaneously over a few months. Treatment is usually unnecessary. If desired, the lesions can be treated effectively with topical antifungals, and/or benzoyl peroxide.

INFANTILE ACNE
Infantile acne usually manifests between 3 mo and 2 yr of age, more commonly in boys than in girls. Acne lesions are more numerous, pleomorphic, severe, and persistent than in neonatal acne (Fig. 669-9). Open and closed comedones predominate on the face. Papules and pustules occur frequently, but only occasionally do nodulocystic lesions develop. Pitted scarring is seen in 10-15%. The course may be relatively brief, or the lesions may persist for many months or years, although the eruption generally resolves by age 4 yr. Use of topical benzoyl peroxide gel and tretinoin usually clears the eruption within a few weeks. Oral erythromycin is occasionally necessary. A child with refractory acne warrants a search for an abnormal source of androgens, such as a virilizing tumor or congenital adrenal hyperplasia.

TROPICAL ACNE
A severe form of acne occurs in tropical climates and is believed to be caused by the intense heat and humidity. Hydration of the pilosebaceous duct pore may accentuate blockage of the duct. Affected individuals tend to have an antecedent history of adolescent acne that is quiescent at the time of the eruption. Lesions occur mainly on the entire back, chest, buttocks, and thighs, with a predominance of suppurating papules and nodules. Secondary infection with S. aureus may be a complication. The eruption is refractory to acne therapy if the environmental factors are not eliminated.

ACNE CONGLOBATA
Acne conglobata is a chronic progressive inflammatory disease that occurs mainly in men, and more commonly in white than in black individuals, but it may begin during adolescence. Patients usually have a history of preceding acne vulgaris. The principal lesion is the nodule, although there is often a mixture of comedones with multiple pores, papules, pustules, nodules, cysts, abscesses, and subcutaneous destruction with formation of multichanneled sinus tracts. Severe scarring is characteristic. The face is relatively spared, but in addition to the back and chest, the buttocks, abdomen, arms, and thighs may be involved. Constitutional symptoms and anemia may accompany the inflammatory process. Coagulase-positive staphylococci and β-hemolytic streptococci are frequently cultured from lesions but do not appear to be primarily involved in the pathogenesis. Acne conglobata occasionally occurs in association with hidradenitis suppurativa and dissecting cellulitis of the scalp (as the follicular occlusion triad) and may be complicated by erosive arthritis and ankylosing spondyloarthropathy. Endocrinologic studies are not revealing. Routine acne therapy is generally ineffective. Systemic therapy with a corticosteroid may be required to suppress the intense inflammatory activity. Isotretinoin is the most effective form of therapy for some patients but may produce a flare after its initiation.

ACNE FULMINANS (ACUTE FEBRILE ULCERATIVE ACNE)
Acne fulminans is characterized by abrupt onset of extensive inflammatory, tender ulcerative acniform lesions on the back and chest of male teenagers. The distinctive feature is the tendency for large nodules to form exudative, necrotic, ulcerated, crusted plaques. Lesions often spare the face and heal with scarring. A preceding history of mild papulopustular or nodular acne is noted in most patients. Constitutional symptoms and signs are common, including fever, dehydration, arthralgias, myalgias, weight loss, and leukocytosis. Blood cultures are sterile. Lesions of erythema nodosum sometimes develop on the shins. Osteolytic bone lesions may develop in the clavicle, sternum, and epiphyseal growth plates; affected bones appear normal or have slight sclerosis or thickening on healing. Salicylates may be helpful for the myalgias, arthralgias, and fever. Corticosteroids (1 mg/kg of
prednisone) are started first. Then 1 wk later, isotretinoin (0.5-1.0 mg/kg) is added. Dapsone may be effective if isotretinoin cannot be used. The corticosteroid dosage is tapered over approximately 6 wk. Antibiotics are not indicated unless there is evidence of secondary infection. Compared with acne conglobata, acne fulminans occurs in younger patients, is more explosive in onset, more commonly has associated constitutional symptoms and ulcerated crusted lesions, and less commonly has multiheaded comedones or involves the face.

Bibliography is available at Expert Consult.
Chapter 670  
Tumors of the Skin
Kari L. Martin

See also Chapters 506.2 and 596.

EPIDERMAL INCLUSION CYST (EPIDERMOID CYST)
Epidermoid cysts are the nodules most commonly seen in children. Such a cyst is a sharply circumscribed, dome-shaped, firm, freely movable, skin-colored nodule (Fig. 670-1) often with a central dimple or punctum that is a plugged, dilated pore of a pilosebaceous follicle. Epidermoid cysts form most frequently on the face, neck, chest, or upper back and may periodically become inflamed and infected secondarily, particularly in association with acne vulgaris. The cyst wall may also rupture and induce an inflammatory reaction in the dermis. The wall of the cyst is derived from the follicular infundibulum. A mass of layered keratinized material that may have a cheesy consistency fills the cavity. Epidermoid cysts may arise from occlusion of pilosebaceous follicles, from implantation of epidermal cells into the dermis as a result of an injury that penetrates the epidermis, and from rests of epidermal cells. Multiple epidermoid cysts may be present in Gardner syndrome and the nevoid basal cell carcinoma syndrome. Excision of the cysts with removal of the entire sac and its contents is indicated, particularly if the cyst becomes recurrently infected. A fluctuant, infected cyst should be treated with antibiotics or intralesional corticosteroids. After the inflammation subsides, the cyst should be removed.

MILIUM
Milium is a 1-2 mm, firm, pearly white or yellowish, subepidermal keratin cyst. Milia in newborns is discussed in Chapter 647. Secondary milia occur in association with subepidermal blistering diseases, after dermabrasion or other injury to the skin. They are retention cysts caused by hyperproliferation of injured epithelium and are indistinguishable histopathologically from primary milia. Those that develop after blistering usually arise from the eccrine sweat duct, but they may develop from the hair follicle, sebaceous duct, or epidermis. A milium body differs from an epidermoid cyst only in its small size and superficial location.

FIBROFOLLICULOMAS
These lesions usually appear in late adolescents or in young adults and are characterized by multiple dome-shaped clear-white papules appearing on the nose, cheeks, and neck, and at times the trunk or ears (Fig. 670-2). They are associated with the familial cancer syndrome of Birt-Hogg-Dubé, an autosomal dominant disorder that results from a mutation in the folliculin (FLCN) gene. Associated features include pulmonary cysts, pneumothorax, renal cell carcinoma, and other benign or malignant tumors.

PILAR CYST (TRICHILEMMAL CYST)
Pilar cyst may be clinically indistinguishable from an epidermoid cyst. It manifests as a smooth, firm, mobile nodule, predominantly on the scalp (Fig. 670-3). Pilar cysts occasionally develop on the face, neck, or trunk. A cyst may become inflamed and may occasionally suppurate and ulcerate. The cyst wall is composed of epithelial cells with indistinct intercellular bridges. The peripheral cell layer of the wall shows a palisade arrangement, which is not seen in an epidermoid cyst. No granular layer is present. The cyst cavity contains homogeneous eosinophilic keratinous material, and foci of calcification are seen in 25% of cases. The propensity for development of pilar cysts may be inherited in an autosomal dominant manner. More than one cyst generally develops in a patient. Numerous pilar and epidermoid cysts, desmoid tumors, fibromas, lipomas, or osteomas may be associated with colonic polyposis or adenocarcinoma in Gardner syndrome. Pilar cysts shell out easily from the dermis.

PILOMATRICOMA
The second most common nodule seen in children, pilomatricoma is a benign tumor that manifests as a 3-30 mm, firm, solitary, deep dermal or subcutaneous tumor on the head, neck, or upper extremities. The overlying epidermis is usually normal. The tumor may occasionally be located more superficially, however, tinging the overlying skin.
blue-red (Fig. 670-4). Multiple pilomatricomas are seen in myotonic dystrophy, Gardner syndrome, Rubinstein-Taybi syndrome, and Turner syndrome. In general, however, pilomatricomas are not hereditary. Histopathologically, irregularly shaped islands of epithelial cells are embedded in a cellular stroma. Calcium deposits are found in 75% of tumors. Pilomatricomas are caused by mutations in β-catenin.

TRICHOEPITHELIOMA
A 2-8 mm, smooth, round, firm, skin-colored papule, trichoepithelioma is derived from an immature hair follicle. Trichoepitheliomas generally occur singly on the face in childhood or early adulthood. Multiple trichoepitheliomas are inherited autosomal dominantly (type 1: CYLD gene; type 2: 9p21 gene currently unidentified), appear in childhood or at puberty, and gradually increase in number on the nasofacial folds, nose, forehead, and upper lip and, occasionally, on the scalp, neck, and upper trunk. Microscopically, these benign tumors are characterized by horn cysts composed of a fully keratinized center surrounded by basophilic cells in an adenoid network. Topical imiquimod therapy may be beneficial. Surgical excision is the only other therapy.

ERUPTIVE VELLUS HAIR CYSTS
Eruptive vellus hair cysts are 1-3 mm, asymptomatic, soft, skin-colored follicular papules on the central chest (Fig. 670-5). They may become crusted or umbilicated. Abnormal vellus hair follicles become occluded at the level of the infundibulum, resulting in retention of hairs within an epithelium-lined cystic dilation of the proximal part of the follicle. Most cases are chronic, but spontaneous regression has been reported.

STEATOCYSTOMA MULTIPLEX
An autosomal dominant (KRT17 gene) condition, steatocystoma multiplex usually manifests in adolescence or early adulthood as numerous soft to firm cystic nodules that are adherent to the underlying skin and are 3 mm to 3 cm in diameter. When punctured, the cysts may drain oily or cheesy material. Sites of predilection include the sternal region, axillae, arms, and scrotal skin. The multiply folded cyst wall is lined on the luminal side with a thick, homogeneous, eosinophilic horny layer and lacks a granular layer. Flattened sebaceous gland lobules are often visible in the cyst wall, and lanugo hairs may be present in the cystic cavity.

SYRINGOMA
The benign tumors known as syringomas are soft, small, skin-colored or yellowish brown papules that develop on the face, particularly in the periocular regions (Fig. 670-6). Other sites of predilection include the axillae and umbilical and pubic areas. They often develop during puberty and are more frequent in females. Eruptive syringomas develop in crops over the anterior trunk during childhood or adolescence. A
syringomas are of cosmetic significance only. Sparse lesions may be excised, but they are often too numerous to remove.

INFANTILE DIGITAL FIBROMA
Infantile digital fibroma is a smooth, firm, erythematous or skin-colored nodule on the dorsal or lateral surface of a distal phalanx of a finger or toe. More than 80% of tumors occur in infancy. They may be present at birth. Lesions may be solitary or multiple and may manifest as “kissing” tumors on opposing digits. They are usually asymptomatic, but flexion deformity of the digits may occur. Clinically, the lesion resembles a fibroma, leiomyoma, angiofibroma, acquired digital fibrokeratoma, accessory digit, or mucous cyst. The diagnosis is confirmed by the finding of numerous spindle-shaped fibroblasts that contain small, round, dense, eosinophilic cytoplasmic inclusion bodies composed of collections of actin microfilaments. Local recurrence after simple excision of this tumor has been reported in 75% of patients. Because the tumor does not metastasize and may regress spontaneously in 2-3 yr, a course of expectant observation is advised. If functional impairment or flexion deformity of the digit becomes apparent, prompt full excision of the tumor is indicated.

DERMATOFIBROMA (HISTIOCYTOMA)
A benign dermal tumor, dermatofibroma may be pedunculated, nodular (Fig. 670-7), or flat and is usually well circumscribed and firm but occasionally feels soft on palpation. The overlying skin is usually hyperpigmented, may be shiny or keratotic, and dimples when the tumor is pinched. Dermatofibromas range in size from 0.5-10.0 mm, arise most frequently on the limbs, and are usually asymptomatic but may occasionally be pruritic. They are composed of fibroblasts, young and mature collagen, capillaries, and histiocytes in varying proportions, forming a nodule in the dermis that has poorly defined edges. The cause of these tumors is unknown, but trauma such as an insect bite or folliculitis appears to induce reactive fibroplasia. The differential diagnosis includes epidermal inclusion cyst, juvenile xanthogranuloma, hypertrophic scar, and neurofibroma. Dermatofibromas may be excised or left intact, according to the patient's preference. They usually persist indefinitely.

JUVENILE XANTHOGRANULOMA
A firm, dome-shaped, yellow, pink, or orange papule or nodule (Fig. 670-8), juvenile xanthogranuloma varies from 5 mm to approximately 4 cm in diameter. The average age at onset is 2 yr. These nodules are 10 times more common in white than in African-American individuals. Sites of predilection are the scalp, face, and upper trunk, where they may erupt in profusion or remain as solitary lesions. Nodular lesions may appear on the oral mucosa. Mature lesions are characterized histopathologically by a dermal infiltrate of lipid-laden histiocytes, admixed inflammatory cells, and Touton giant cells. The lesions may clinically resemble papulonodular urticaria pigmentosa, dermatofibromas, or xanthomas of hyperlipoproteinemia, but can be distinguished from these entities histopathologically.

Affected infants are nearly always otherwise normal, and blood lipid values are not elevated. Café-au-lait macules are found on 20% of patients with juvenile xanthogranuloma. Xanthogranulomatous infiltrates occur occasionally in ocular tissues. This process may result in glaucoma, hyphema, uveitis, heterochromia iridis, iritis, or sudden proptosis. Age less than 2 yr, multiple lesions, and periocular location may heighten concerns for intraocular involvement. There appears to be an association among juvenile xanthogranuloma, neurofibromatosis, and childhood leukemia, most frequently juvenile chronic myelogenous leukemia. There is no need to remove the benign lesions of juvenile xanthogranuloma because most of them regress spontaneously in the 1st few yr. Residual pigmentation and atrophy may result.

LIPOMA
A benign collection of fatty tissue, lipoma appears on the trunk, neck, or proximal portions of the limbs. Lipomas are soft, compressible, lobulated, subcutaneous masses. Multiple lesions may occur occasionally, as in Gardner syndrome. Atrophy, calcification, liquefaction, or xanthomatous change may sometimes complicate their course. A lipoma is composed of normal fat cells surrounded by a thin connective tissue capsule. Lipomas represent a cosmetic defect and may be surgically excised. Multiple lipomas, identical to those that occur singly, are inherited in an autosomal dominant fashion and often appear by the 3rd decade in patients with familial multiple lipomatosis. Lipomas may appear intraabdominally, intramuscularly, and subcutaneously. Congenital lipomatosis manifests in the 1st few mo of life as large subcutaneous fatty masses on the chest, with extension into skeletal muscle. Congenital lipomatosis can also be a manifestation of Proteus syndrome (overgrowth/hyperplasia skin, connective tissue, mutation in AKT1). Angiolipomas usually manifest as numerous painful subcutaneous nodules on the arms and trunk.

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal-spinal anomalies) is usually a sporadic disorder with an asymmetric truncal lipomatous mass present at birth. Additional features include macrodactyly, vascular malformations (low flow), linear epidermal nevus and renal anomalies. The differential diagnosis includes Proteus, Klippel-Trenaunay, and Bannayan-Riley-Ruvalcaba syndrome.

BASAL CELL CARCINOMA
Basal cell carcinoma is very rare in children in the absence of a predisposing condition, such as nevoid basal cell carcinoma syndrome, xeroderma pigmentosum, nevus sebaceus of Jadassohn, arsenic intake, or exposure to irradiation. The lesions are smooth, pearly, pink, telangiectatic papules that enlarge slowly and may bleed or ulcerate. Sites of predilection are the face, scalp, and upper back. The differential
excavatum, pes cavus, and muscular hypotonia. The syndrome is caused by mutations in the tyrosine kinase domain of the RET gene. Patients have thick, patulous lips and soft-tissue prognathism simulating acromegaly. Multiple mucosal neuromas or neurofibromas appear as pink, pedunculated or sessile nodules on the anterior third of the tongue, at the commissures of the lips, and on the buccal mucosa and palpebral conjunctiva. Various ophthalmologic defects and intestinal ganglioneuromatosis with recurrent diarrhea are additional common findings. There is a high incidence of medullary thyroid carcinoma in association with high calcitonin levels, pheochromocytoma, and hyperparathyroidism in patients with this syndrome. Periodic screening tests for the associated malignant tumors are mandatory.

**NEVOID BASAL CELL CARCINOMA SYNDROME (BASAL CELL NEVUS SYNDROME, GORLIN SYNDROME)**

The autosomal dominant entity known as nevoid basal cell carcinoma syndrome is caused by mutations in the **PTCH1** and **PTCH2** (**patched**) genes. These tumor-suppressor genes, part of the hedgehog signaling pathway, are important in determining embryonic patterning and cell fate in a number of structures in the developing embryo. Mutations in human patched genes produce dysregulation of several genes involved in organogenesis and carcinogenesis. Consequently, the syndrome includes a wide spectrum of defects involving the skin, eyes, central nervous and endocrine systems, and bones. The predominant features are early-onset basal cell carcinomas and mandibular cysts. Approximately 20% of those in whom a basal cell carcinoma develops before age 19 yr have this syndrome. Basal cell carcinomas appear between puberty and age 35 yr, erupting in crops of tumors that vary in size, color, and number, and may be difficult to distinguish from other types of skin lesions. Sites of predilection are the peri-orbital skin, nose, malar areas, and upper lip, but the lesions can develop on the trunk and limbs and are not restricted to sun-exposed areas. Ulceration, bleeding, crusting, and local invasion can occur. Small milia, epidermal cysts, pigmented lesions, hirsutism, and palmar and plantar pits are additional cutaneous findings.

The facies of patients with this syndrome are characterized by temporoparietal bossing, prominent supraorbital ridges, a broad nasal root, ocular hypertelorism or dystopia canthorum, and prognathism. Keratinized cysts (odontogenic keratocysts) in the maxilla and mandible occur in most patients. They range in size from a few millimeters to several centimeters, may result in maldevelopment of the teeth, and cause pain, swelling of the jaw, facial deformity, bone erosion, pathologic fractures, and suppurating sinus tracts. Osseous defects such as anomalous rib development, spina bifida, kyphoscoliosis, and brachymetacarpalism occur in 60% of patients, and ocular abnormalities including cataracts, glaucoma, coloboma, strabismus, and blindness occur in approximately 25%. Some males have hypogonadism, and the testes are absent or undescended. Kidney malformations have also been reported. Neurologic manifestations include calcification of the falk, seizures, mental retardation, partial agenesis of the corpus callosum, hydrocephalus, and nerve deafness. The incidence of medulloblastoma, ameloblastoma of the oral cavity, fibrosarcoma of the jaw, teratoma, cystadenoma, cardiac fibroma, ovarian fibroma, and fetal onset rhabdomyoma is higher in patients with nevoid basal cell carcinoma syndrome.

**Treatment** of these patients requires the participation of various specialists according to individual clinical problems. Basal cell carcinomas should not be treated with irradiation. Most of the basal cell carcinomas have a clinically benign course, and it is often impossible to remove them all. Those with an aggressive growth pattern and those on the central areas of the face, however, should be removed promptly. Treatment options include surgery, Mohs micrographic surgery, laser ablation, cryotherapy, photodynamic therapy, topical 5% imiquimod and oral retinoids (0.5–1.0 mg/kg/day). Vismodegib, which inhibits smoothened protein in the hedgehog pathway, is a targeted therapy available for unresectable basal cell carcinomas. Genetic counseling is also indicated.

**MUCOSAL NEUROMA SYNDROME (MULTIPLE ENDOCRINE NEOPLASIA TYPE IIB)**

Mucosal neuroma syndrome, an autosomal dominant trait, is characterized by an asthenic or marfanoid habitus with scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The syndrome is caused by mutations in the tyrosine kinase domain of the RET gene. Patients have thick, patulous lips and soft-tissue prognathism simulating acromegaly. Multiple mucosal neuromas or neurofibromas appear as pink, pedunculated or sessile nodules on the anterior third of the tongue, at the commissures of the lips, and on the buccal mucosa and palpebral conjunctiva. Various ophthalmologic defects and intestinal ganglioneuromatosis with recurrent diarrhea are additional common findings. There is a high incidence of medullary thyroid carcinoma in association with high calcitonin levels, pheochromocytoma, and hyperparathyroidism in patients with this syndrome. Periodic screening tests for the associated malignant tumors are mandatory.

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

Joel C. Joyce

ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by an inability to absorb sufficient zinc from the diet. The genetic defect is in the intestinal zinc-specific transporter gene SLC39A4. Initial signs and symptoms usually occur in the 1st few mo of life, often after weaning from breast milk to cow’s milk. The cutaneous eruption consists of vesiculobullous, eczematous, dry, scaly, or psoriasiform skin lesions symmetrically distributed in the perioral, acral, and perineal areas (Fig. 671-1) and on the cheeks, knees, and elbows (Fig. 671-2). The hair often has a peculiar, reddish tint, and alopecia of some degree is characteristic. Ocular manifestations include photophobia, conjunctivitis, blepharitis, and corneal dystrophy detectable by slit-lamp examination. Associated manifestations include chronic diarrhea, stomatitis, glossitis, paronychia, nail dystrophy, growth retardation, irritability, delayed wound healing, intercurrent bacterial infections, and superinfection with Candida albicans. Lymphocyte function and free radical scavenging are impaired. Without treatment, the course is chronic and intermittent but often relentlessly progressive. When the disease is less severe, only growth retardation and delayed development may be apparent.

The diagnosis is established by the constellation of clinical findings and detection of a low plasma zinc concentration. A serum zinc level less than 50 µg/dL is suggestive, but not diagnostic, of acrodermatitis enteropathica. Levels of alkaline phosphatase, a zinc-dependent enzyme, may also be decreased. Histopathologic changes in the skin are nonspecific and include parakeratosis and pallor of the upper epidermis. The variety of manifestations of the syndrome may be because zinc has a role in numerous metabolic pathways, including those of copper, protein, essential fatty acids, and prostaglandins, and that zinc is incorporated into many zinc metalloenzymes.

Oral therapy with zinc compounds is the treatment of choice. Replacement for individuals with inherited acrodermatitis enteropathica is with 3 mg/kg/24 hr of elemental zinc found in zinc sulfate, gluconate, or acetate (i.e., 220 mg of zinc sulfate contains 50 mg of elemental zinc). Zinc gluconate carries less risk of gastrointestinal distress. Plasma zinc levels should be monitored every 3-6 mo, however, to individualize the dosage. Zinc therapy rapidly abolishes the manifestations of the disease. A syndrome resembling acrodermatitis enteropathica has been observed in patients with secondary zinc deficiency resulting from long-term total parenteral nutrition without
supplemental zinc or to chronic malabsorption syndromes. A rash similar to that of acrodermatitis enteropathica has also been reported in infants fed breast milk that is low in zinc and in those with maple syrup urine disease, organic aciduria, methylmalonic acidemia, biotinidase deficiency, essential fatty acid deficiency, severe protein malnutrition (kwashiorkor), and cystic fibrosis. For those individuals with acquired zinc deficiency, oral replacement with 0.5-1.0 mg/kg/24 hr of elemental zinc should be undertaken and the cause of underlying malnutrition should be addressed.

**ESSENTIAL FATTY ACID DEFICIENCY**

Essential fatty acid deficiency causes a generalized, scaly dermatitis composed of thickened, erythematous, desquamating plaques. Individuals may also show failure-to-thrive, growth retardation, alopecia, thrombocytopenia, and poor wound healing. The eruption has been induced experimentally in animals fed a fat-free diet and has been observed in patients with chronic severe malabsorption, such as in short-gut syndrome, and in those sustained on a fat-free diet or fat-free parenteral alimentation. Linoleic acid (18:2 n-6) and arachidonic acid (20:4 n-6) are deficient, and an abnormal metabolite, 5,8,11-eicosatrienoic acid (20:3 n-9), is present in the plasma. Alterations in the triene : tetraene ratio are diagnostic (arachidonic acid : eicosatrienoic acid ratio greater than 0.4 or linoleic acid : arachidonic acid ratio greater than 2.3). The horny layer of the skin contains microscopic cracks, the barrier function of the skin is disturbed, and trans-epidermal water loss is increased. Topical application of linoleic acid, which is present in sunflower seed and safflower oils, may ameliorate the clinical and biochemical skin manifestations. Oral and/or parenteral therapy can also be considered. Appropriate nutrition should be provided.

**KWASHIORKOR**

Severe protein and essential amino acid deprivation in association with adequate caloric intake can lead to kwashiorkor, particularly at the time of weaning to a diet that consists primarily of corn, rice (or rice milk), or beans (see Chapter 46). Children can be fed such a restricted diet for cultural reasons or because of misdiagnosis on the part of the child’s parents or healthcare providers of perceived food allergies. Diffuse fine reddish brown scaling (enamel/flaky paint sign) is the classic cutaneous finding. In severe cases, erosions and linear fissures
develop (Fig. 671-3). Nails are thin and soft, and hair is sparse, thin, and depigmented, sometimes displaying a “flag sign” consisting of alternating light and dark bands that reflect alternating periods of adequate and inadequate nutrition. The cutaneous manifestations may closely resemble those of acrodermatitis enteropathica, however; edema of the extremities and face (“moon facies”) and a protuberant abdomen (“pot belly”) are key features uniformly observed in kwashiorkor. The serum zinc level is often deficient, and in some cases, skin lesions of kwashiorkor heal more rapidly when zinc is applied topically.

**CYSTIC FIBROSIS**

See Chapter 403.

Protein-calorie malnutrition develops in 5-10% of patients with cystic fibrosis. Rash in infants with cystic fibrosis and malnutrition is rare but may appear by age 6 mo. The initial eruption consists of scaling, erythematous papules and progresses in 1-3 mo to extensive desquamating plaques. The rash is accentuated around the mouth and perineum and on the extremities (lower > upper). Alopecia may be present, but mucous membranes and nails are uninvolved.

**PELLAGRA**

See Chapter 49.

Pellagra manifests as edema, erythema, and burning of sun-exposed skin on the face, neck, and dorsal aspects of the hands, forearms, and feet. Lesions of pellagra may also be provoked by burns, pressure, friction, and inflammation. The eruption on the face frequently follows a butterfly distribution, and the dermatitis encircling the neck has been termed “Casal’s necklace.” Blisters and scales develop, and the skin increasingly becomes dry, rough, thickened, cracked, and hyperpigmented. Skin infections may be unusually severe. Pellagra develops in patients with insufficient dietary intake or malabsorption of niacin and/or tryptophan. Administration of isoniazid, 6-mercaptopurine, or 5-fluorouracil may also produce pellagra. Hartnup disease (see Chapter 85), caused by a mutation in SLC6A19 that encodes a neutral amino acid transporter, is a rare autosomal recessive disorder that presents in infancy with a “pellagra-like syndrome” as a result of decreased absorption of tryptophan. Nicotinamide supplementation and sun avoidance are the mainstays of therapy in pellagra.

**SCURVY (VITAMIN C OR ASCORBIC ACID DEFICIENCY)**

See Chapter 50.

Scurvy manifests initially as follicular hyperkeratosis, coiling of the hair on the upper arms, back, buttocks, and lower extremities. Other features are perifollicular erythema and hemorrhage, particularly on the legs and advancing to involve large areas of hemorrhage; swollen, erythematous gums; stomatitis; and subperiosteal hematomas. In children, the most common risk factors are behavioral or psychiatric disease that results in poor nutrition. The best method of confirmation of a clinical diagnosis of scurvy is a trial of vitamin C supplementation.

**VITAMIN A DEFICIENCY**

See Chapter 48.1.

Vitamin A deficiency manifests initially as impairment of visual adaptation to the dark. Cutaneous changes include xerosis and hyperkeratosis and hyperplasia of the epidermis, particularly the lining of hair follicles and sebaceous glands. In severe cases, desquamation may be prominent.

*Bibliography is available at Expert Consult.*
Bibliography


Section 1
Orthopedic Problems

Chapter 672
Growth and Development
Keith D. Baldwin, Lawrence Wells, and John P. Dormans

Statistically, normal is defined as 95% of a population that falls within 2 SD of the mean from any given measurement. Statistically normal should not be confused with ideal in any given person or parent’s mind. Table 672-1 lists terms used to describe some common deviations from normal. Congenital anomalies can be categorized into production problems and packaging problems. Production problems include abnormalities caused by malformation, dysplasia, or disruption that will not spontaneously resolve (see Chapter 108). Packaging problems include deformations caused by mechanical causes including in utero positioning and molding, and they usually resolve with time.

IN UTERO POSITIONING
In utero positioning produces temporary joint and muscle contractures and affects the torsional alignment of the long bones, particularly those of the lower extremities. Normal full-term newborns can have up to 20-30 degree hip and knee flexion contractures. These contractures tend to resolve by 4-6 mo of age. The newborn hip externally rotates and affects the torsional alignment of the long bones, particularly those of the lower extremities. Normal full-term newborns can have up to 20-30 degree hip and knee flexion contractures. These contractures tend to resolve by 4-6 mo of age. The newborn hip externally rotates and affects the torsional alignment of the long bones, particularly those.

Table 672-1 Terminologies for Deviations

<table>
<thead>
<tr>
<th>TERMINOLOGY</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>Congenital</td>
<td>Anomaly that is apparent at birth</td>
</tr>
<tr>
<td>Deformation</td>
<td>A normally formed structure that is pushed out of shape by mechanical forces</td>
</tr>
<tr>
<td>Deformity</td>
<td>A body part altered in shape from normal, outside the normal range</td>
</tr>
<tr>
<td>Developmental</td>
<td>A deviation that occurs over time; one that might not be present or apparent at birth</td>
</tr>
<tr>
<td>Disruption</td>
<td>A structure undergoing normal development that stops developing or is destroyed or removed</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>A tissue that is abnormal or wrongly constructed</td>
</tr>
<tr>
<td>Malformation</td>
<td>A structure that is wrongly built; failure of embryologic development or differentiation resulting in abnormal or missing structures</td>
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GROWTH AND DEVELOPMENT
Consideration of growth and development helps to formulate treatment strategies designed to preserve or restore normal growth potential. Growth is subject to many variables including genetics, nutrition, general health, endocrine status, mechanical forces, and physiologic age. Growth also varies between 2 anatomic regions and even between 2 bones of the same region.

Bone formation or ossification occurs in 2 different ways. In enchondral ossification, mesenchymal cells undergo chondrogenesis to form cartilage that matures to become bone. Most bones in the axial and appendicular skeleton are formed in this manner. In intramembranous ossification, osteoblasts are formed by direct differentiation of mesenchymal cells into bone. Flat bones of the skull and clavicle are examples of this pattern of bone formation.

CENTERS OF OSSIFICATION
At the beginning of the fetal period the chondrocytes in the midshaft of the long bones form the primary centers of growth from which the bone eventually lengthens. Secondary centers of ossification appear in the chondroepiphysis and mostly appear postnatally. They direct the formation of bone throughout growth, particularly joint development. The ossification centers that are typically present at birth are the distal femur, proximal tibia, calcaneus, and talus.

Anatomic Locations: Descriptive Terms
Typical long bones are divided into the physis, epiphysis, metaphysis, diaphysis, and perichondrial ring (Fig. 672-1). The physis is the growth plate located at the end of bone. The epiphysis is typically a secondary ossification center that contributes to joint development. The metaphysis is the bone adjacent to the physis on the side away from the joint. The diaphysis is the central part or shaft of long bones. The perichondrial ring contributes to appositional growth.

The articular cartilage also contributes to the growth of the epiphysis. The perichondrial ring, which surrounds the physis, and the perichondrium around the epiphyses and periosteum, which surrounds the metaphysis and diaphyseal regions of the bone, contribute to appositional or circumferential growth. Bones without physis (pelvis, scapulae, carpals, tarsals) grow by appositional bone growth from their surrounding perichondrium and periosteum. Other bones (metacarpals, metatarsals, phalanges, spine) grow by a combination of appositional and enchondral ossification.

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**Growth and Development**

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**Figure 672-1** Diagram showing typical long bone divisions.
Important Growth and Developmental Milestones

Table 672-2 summarizes some important musculoskeletal growth considerations.

Growth Patterns in Upper and Lower Extremities

The upper extremity grows longitudinally, primarily from physes of the proximal humeral physis and the distal radial and ulnar physes. In the lower extremity, most of the longitudinal growth occurs around the knee, in the distal femoral and the proximal tibial physes (Fig. 672-2).

In the hip joint, the acetabulum forms with the convergence of 3 primary ossification centers: ischium, ilium, and pubis.

Gait/Functional Maturation

Functional mobility develops in infants in a predictable fashion (Table 672-3). Failure to achieve functional milestones is an indication for referral to a neurologist to determine if a central nervous system problem exists. Central nervous system maturation contributes significantly to the development of gait. In early ambulation (at 8-15 mo), the child usually has a wide-based gait with hyperflexion of hips and knees, and initial contact with the heel. By the age of 2 yr, the wide gait diminishes, reciprocal arm swing begins, and there is increased stride length and velocity. Adult fluid gait patterns usually start developing by 3 yr and mature to an adult-like pattern by age 7 yr.

Bibliography is available at Expert Consult.
Bibliography


A detailed history and thorough physical examination are critical to the evaluation of a child with an orthopedic problem. The child’s family and acquaintances are important sources of information, especially in younger children and infants. Appropriate radiographic imaging and, occasionally, laboratory testing may be necessary to support the clinical diagnosis.
HISTORY
A comprehensive history should include details about the prenatal, perinatal, and postnatal periods. Prenatal history should include maternal health issues: smoking, prenatal vitamins, illicit use of drugs or narcotics, alcohol consumption, diabetes, rubella, and sexually transmitted infections. The child’s prenatal and perinatal history should include information about the length of pregnancy, length of labor, type of labor (induced or spontaneous), presentation of fetus, evidence of any fetal distress at delivery, requirements of oxygen following the delivery, birth length and weight, Apgar score, muscle tone at birth, feeding history, and period of hospitalization. In older infants and young children, evaluation of developmental milestones for posture, locomotion, dexterity, social activities, and speech are important. Specific orthopedic questions should focus on joint, muscular, appendicular, or axial skeleton complaints. Information regarding pain or other symptoms in any of these areas should be appropriately elicited (Table 673-1). The family history can give clues to heritable disorders. It also can forecast expectations of the child’s future development and allow appropriate interventions as necessary.

PHYSICAL EXAMINATION
The orthopedic physical examination includes a thorough examination of the musculoskeletal system along with a comprehensive neurologic examination. The musculoskeletal examination includes inspection, palpation, and evaluation of motion, stability, and gait. A basic neurologic examination includes sensory examination, motor function, and reflexes. The orthopedic physical examination requires basic knowledge of anatomy of joint range of motion, alignment, and stability. Many common musculoskeletal disorders can be diagnosed by the history and physical examination alone. One screening tool that has been useful in adults has now been adapted and evaluated for use in children, the pediatric gait, arms, legs, spine (pGALS) test, the components of which are listed in Figure 673-1.

Inspection
Initial examination of the child begins with inspection. The clinician should use the guidelines listed in Table 673-2 during inspection.

Palpation
Palpation of the involved region should include assessment of local temperature and tenderness; assessment for a swelling or mass, spasticity or contracture, and bone or joint deformity; and evaluation of anatomic axis of limb and of limb lengths.

Contractures are a loss of mobility of a joint from congenital or acquired causes and are caused by periarticular soft-tissue fibrosis or involvement of muscles crossing the joint. Congenital contractures are common in arthrogryposis (see Chapter 682). Spasticity is an abnormal increase in tone associated with hyperreflexia and is common in cerebral palsy.

Deformity of the bone or joint is an abnormal fixed shape or position from congenital or acquired causes. It is important to assess the type of deformity, its location, and degree of deformity upon clinical examination. It is also important to assess whether the deformity is fixed or can be passively or actively corrected and whether there is any associated muscle spasm, local tenderness, or pain on motion. Classification of the deformity depends on the plane of deformity: varus (away from midline) or valgus (apex toward midline), or recurvatum (backward curvature) or flexion deformity (sagittal plane). In the axial skeleton, especially the spine, deformity can be defined as scoliosis, kyphosis, hyperlordosis, and kyphoscoliosis.

Range of Motion
Active and passive joint motion should be assessed, recorded, and compared to the opposite side. Objective evaluation should be done with a goniometer and recorded.

Vocabulary for direction of joint motion is as follows:
Abduction: Away from the midline
Adduction: Toward the midline
Flexion: Movement of bending from the starting position
Extension: Movement from bending to the starting position
Supination: Rotating the forearm to face the palm upward
Pronation: Rotating the forearm to face the palm downward
Inversion: Turning the hindfoot inward
Eversion: Turning the hindfoot outward
Plantarflexion: Pointing the toes away from the body (toward the floor)
Dorsiflexion: Pointing the toes toward the body (toward the ceiling)
Internal rotation: Turning inward toward the axis of the body
External rotation: Turning outward away from the axis of the body

<table>
<thead>
<tr>
<th>Table 673-1</th>
<th>Characterization of Pain and Presenting Symptom</th>
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</thead>
<tbody>
<tr>
<td>Location:</td>
<td>Whether pain is localized to a particular segment or involves a larger area</td>
</tr>
<tr>
<td>Intensity:</td>
<td>Usually on a pain scale of 1-10</td>
</tr>
<tr>
<td>Quality:</td>
<td>Tumor pain is often unrelenting, progressive, and often present during the night. Pain at night particularly suggests osteoid osteoma. Pain in inflammation and infection is usually continuous</td>
</tr>
<tr>
<td>Onset:</td>
<td>Was it acute and related to specific trauma or was it insidious? Acute pain and history of trauma are more commonly associated with fractures</td>
</tr>
<tr>
<td>Duration:</td>
<td>Whether transient, only lasting for minutes, or lasting for hours or days. Pain lasting for longer than 3-4 wk suggests a serious underlying problem</td>
</tr>
<tr>
<td>Progress:</td>
<td>Whether static, increasing, or decreasing</td>
</tr>
<tr>
<td>Radiation:</td>
<td>Pain radiating to upper or lower extremities or complaints of numbness, tingling, or weakness require appropriate work-up</td>
</tr>
<tr>
<td>Aggravating factors:</td>
<td>Relationship to any activities such as swimming or diving or any particular position</td>
</tr>
<tr>
<td>Alleviating factors:</td>
<td>Is the pain relieved by rest, heat, and/or medication? Conditions such as spondylosis, Scheuermann disease, inflammatory spondyloarthropathy, muscle pulls, or overuse are improved by bed rest</td>
</tr>
<tr>
<td>Gait and posture:</td>
<td>Disturbances associated with pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 673-2</th>
<th>Guidelines During Inspection of a Child with Musculoskeletal Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The patient should be comfortable with adequate exposure and well-lit surroundings (lest some important physical finding be missed). Infants or young children may be examined on their parent’s lap so that they feel more secure and are more likely to be cooperative.</td>
<td></td>
</tr>
<tr>
<td>• It is important to inspect how the patient moves about in the room before and during the examination, as well as during various maneuvers. Balance, posture, and gait pattern should also be checked.</td>
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</tr>
<tr>
<td>• General examination findings should include inspection for skin rashes, café-au-lait spots, hairy patches, dimples, cysts, tuft of hair, or evidence of spinal midline defects that can indicate serious underlying problems that need review.</td>
<td></td>
</tr>
<tr>
<td>• General body habitus, including signs of cachexia, pallor, and nutritional deficiencies, should be noted.</td>
<td></td>
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<tr>
<td>• Note any obvious spinal asymmetry, axial or appendicular deformities, trunk decompensation, and evidence of muscle spasm or contractures. The forward bending test is valuable in assessing asymmetry and movement of the spine.</td>
<td></td>
</tr>
<tr>
<td>• It is essential to perform and document a thorough neurologic examination. Motor, sensory, and reflex testing should be performed and recorded.</td>
<td></td>
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<tr>
<td>• Any discrepancies in limb lengths, as well as muscle atrophy, should be recorded.</td>
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<tr>
<td>• The range of motion of all joints, their stability, and any evidence of hyperlaxity, peripheral pulsations, and lymphadenopathy should also be noted in all cases.</td>
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</table>
Figure 673-1 The components of pediatric gait, arms, legs, spine (pGALS) screen, with illustration of movement. Screening questions: (1) Do you have any pain or stiffness in your joints, muscles, or back? (2) Do you have any difficulty getting yourself dressed without any help? (3) Do you have any difficulty going up and down stairs? *Additions and amendments to the original adult gait, arms, legs, spine screen. (From Foster HE, Kay LJ, Friswell M, et al: Musculoskeletal screening examination [pGALS] for school-age children based on the adult GALS screen, Arthritis Rheum 55:709–716, 2006.)
Gait Assessment
Children typically begin walking between 8 and 16 mo of age. Early ambulation is characterized by short stride length, a fast cadence, and slow velocity with a wide-based stance. Gait cycle is a single sequence of functions that starts with heel strike, toe off, swing, and heel strike. The 4 events describe 1 gait cycle and include 2 phases: stance and swing. The stance phase is the period during which the foot is in contact with the ground. The swing phase is the portion of the gait cycle during which a limb is being advanced forward without ground contact (see Chapter 672). Normal gait is a symmetric and smooth process. Deviation from the norm indicates potential abnormality and should trigger investigation.

Neurologic maturation is necessary for the development of gait and the normal progression of developmental milestones. A child’s gait changes with neurologic maturation. Infants normally walk with greater hip and knee flexion, flexed arms, and a wider base of gait than older children. As the neurologic system continues to develop in the cephalocaudal direction, the efficiency and smoothness of gait increase. The gait characteristics of a 7 yr old child are similar to those of an adult. When the neurologic system is abnormal (cerebral palsy), gait can be disturbed, exhibiting pathologic reflexes and abnormal movements.

Deviations from normal gait occur in a variety of orthopedic conditions. Disorders that result in muscle weakness (e.g., spina bifida, muscular dystrophy), spasticity (e.g., cerebral palsy), or contractures (e.g., arthrogryposis) lead to abnormalities in gait. Other causes of gait disturbances include limp, pain, torsional variations (in-toeing and out-toeing), toe walking, joint abnormalities, and leg-length discrepancy (Table 673-3).

LIMPING
A thorough history and clinical examination are the first steps toward early identification of the underlying problem causing a limp. Limping can be considered as either painful (antalgic) or painless, with the differential diagnosis ranging from benign to serious causes (septic hip, tumor). In a painful gait, the stance phase is shortened as the child decreases the time spent on the painful extremity. In a painless gait, which indicates underlying proximal muscle weakness or hip instability, the stance phase is equal between the involved and uninvolved sides, but the child leans or shifts the center of gravity over the involved extremity for balance. A bilateral disorder produces a waddling gait. Trendelenburg gait is produced by weak abnormal hip abductors. In single leg stance, a Trendelenburg sign can often be elicited when abductors are weak.

Disorders most commonly responsible for an abnormal gait generally vary based on the age of the patient. The differential diagnosis of limping varies based on age group (Table 673-4) or mechanism (Table 673-5). Neurologic disorders, especially spinal cord or peripheral nerve disorders, can also produce limping and difficult walking. Antalgic gait is predominantly a result of trauma, infection, or pathologic fracture. Trendelenburg gait is generally caused by congenital, developmental, or muscular disorders. In some cases, limping also may be caused by nonskeletal causes such as testicular torsion, inguinal hernia, and appendicitis.

BACK PAIN
Children frequently have a specific skeletal pathology as the cause of back pain. The most common causes of back pain in children are trauma, spondylolysis, spondylolisthesis, and infection (see Table 679-2). Tumor and tumor-like lesions that cause back pain in children are likely to be missed unless a thorough clinical assessment and adequate work-up are performed when required. Nonorthopedic causes of back pain include urinary tract infections, nephrolithiasis, and pneumonia.

**NEUROLOGIC EVALUATION**
A careful neurologic evaluation is a part of every pediatric musculoskeletal examination (see Chapter 590). The assessment should include evaluation of developmental milestones, muscle strength, sensory assessment, muscle tone, and deep tendon reflexes. The neurologic evaluation should also assess the spine and identify any deformity, such as scoliosis and kyphosis, or abnormal spinal mobility. The hips and feet should also be examined specifically, along with torsional abnormalities of the lower extremity, which are vastly more common in the neurologically involved population. Specific peripheral nerve examinations may be necessary.

As the nervous system matures, the developing cerebral cortex normally inhibits rudimentary reflexes that are often present at birth (see Chapter 590). Therefore, persistence of these reflexes can indicate neurologic abnormality. The most commonly performed deep tendon reflex tests include biceps, triceps, quadriceps, and gastrocnemius and soleus tendons. Upper motor neuron signs should also be noted. The

<table>
<thead>
<tr>
<th>Table 673-3</th>
<th>Causes of Abnormal Gait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limp</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Torsional variations</td>
</tr>
<tr>
<td></td>
<td>Toe walking</td>
</tr>
<tr>
<td></td>
<td>Joint abnormalities</td>
</tr>
<tr>
<td></td>
<td>Leg-length discrepancy</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 673-4</th>
<th>Common Causes of Limping According to Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTALGIC</td>
<td>TRENDELENBURG</td>
</tr>
<tr>
<td></td>
<td>LEG-LENGTH DISCREPANCY</td>
</tr>
<tr>
<td>TODDLER (1-3 YR)</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Septic arthritis</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
</tr>
<tr>
<td></td>
<td>Knee</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Diskitis</td>
</tr>
<tr>
<td></td>
<td>Occult trauma</td>
</tr>
<tr>
<td></td>
<td>Toddler’s fracture</td>
</tr>
<tr>
<td></td>
<td>Neoplasia</td>
</tr>
<tr>
<td>CHILD (4-10 YR)</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Septic arthritis</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
</tr>
<tr>
<td></td>
<td>Knee</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Diskitis</td>
</tr>
<tr>
<td></td>
<td>Transient synovitis, hip</td>
</tr>
<tr>
<td></td>
<td>LCBD</td>
</tr>
<tr>
<td></td>
<td>Tarsal coalition</td>
</tr>
<tr>
<td></td>
<td>Rheumatologic disorder</td>
</tr>
<tr>
<td></td>
<td>JRA</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Neoplasia</td>
</tr>
<tr>
<td>ADOLESCENT (11+ YR)</td>
<td>SCFE</td>
</tr>
<tr>
<td></td>
<td>Rheumatologic disorder</td>
</tr>
<tr>
<td></td>
<td>JRA</td>
</tr>
<tr>
<td></td>
<td>Trauma: fracture, overuse</td>
</tr>
<tr>
<td></td>
<td>Tarsal coalition</td>
</tr>
<tr>
<td></td>
<td>Neoplasia</td>
</tr>
</tbody>
</table>

−, Absent; +, present; DDH, developmental dysplasia of the hip; JRA, juvenile rheumatoid arthritis; LCBD, Legg-Calvé-Perthes disease; SCFE, slipped capital femoral epiphysis.

Table 673-5 | Differential Diagnosis of Limping

<table>
<thead>
<tr>
<th>Category</th>
<th>Example Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antalgic Gait</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>Tarsal coalition</td>
</tr>
<tr>
<td>Acquired</td>
<td>Legg-Calvé-Perthes disease</td>
</tr>
<tr>
<td>Trauma</td>
<td>Sprains, strains, contusions</td>
</tr>
<tr>
<td>Fractures</td>
<td>Occult</td>
</tr>
<tr>
<td>Toddler’s fracture</td>
<td>Abuse</td>
</tr>
<tr>
<td><strong>Neoplasia</strong></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>Unicameral bone cyst</td>
</tr>
<tr>
<td>Malignant</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td></td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Subacute</td>
</tr>
<tr>
<td>Diskitis</td>
<td></td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Hip monoarticular synovitis</td>
<td>(toxic transient synovitis)</td>
</tr>
</tbody>
</table>

**Trendelenburg**

- Developmental dysplasia of the hip
- Leg-length discrepancy
- Neuromuscular
- Cerebral palsy
- Poliomyelitis

Table 673-6 | Ashworth Scale of Spasticity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in muscle tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in muscle tone, usually a catch or minimal resistance at end range of motion</td>
</tr>
<tr>
<td>2</td>
<td>Moderate tone throughout range of motion</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in tone; passive range of motion difficult</td>
</tr>
<tr>
<td>4</td>
<td>Rigid in flexion or extension</td>
</tr>
</tbody>
</table>

Table 673-7 | Clinical Scale of Upper-Extremity Motor Control

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypotonic, no volitional motion</td>
</tr>
<tr>
<td>2</td>
<td>Hypertonic, no volitional motion</td>
</tr>
<tr>
<td>3</td>
<td>Mass flexion or extension in response to a stimulus</td>
</tr>
<tr>
<td>4</td>
<td>Patient can initiate movement but results in mass flexion or extension</td>
</tr>
<tr>
<td>5</td>
<td>Slow volitional movement; stress or rapid movement results in mass action</td>
</tr>
<tr>
<td>6</td>
<td>Volitional control of specific joints/muscles</td>
</tr>
</tbody>
</table>

Ashworth scale is often used to grade spasticity (Table 673-6). Upper-extremity motor control is often graded, and these grades are useful both diagnostically and prognostically. Passive range of motion should be assessed to determine contractures (Table 673-7). Localized or diffuse weakness must be determined and documented. A thorough assessment and grading of muscle strength is mandatory in all cases of neuromuscular disorders.

**RADIOGRAPHIC ASSESSMENT**

Plain radiographs are the first step in evaluation of most musculoskeletal disorders. Advanced imaging includes special procedures such as nuclear bone scans, ultrasonography, MRI, CT, and positron emission tomography.

**Plain Radiographs**

Routine radiographs are the first step and consist of anteroposterior and lateral views of the involved area with 1 joint above and below. Comparison views of the opposite side, if uninvolved, may be helpful in difficult situations but are not always necessary. It is important for the clinician to be aware of normal radiographic variants of the immature skeleton. Several synchondroses may be mistaken for fractures. A patient with “normal” plain radiographic appearance but having persistent pain or symptoms might need to be evaluated further with additional imaging studies.

**Nuclear Medicine Imaging**

A bone scan displays physiologic information rather than pure anatomy and relies on the emission of energy from the nucleotide injected into the patient. Indications include early septic arthritis, osteomyelitis, avascular necrosis, tumors (osteoid osteoma), metastatic lesions, occult and stress fractures, and cases of child abuse.

Total-body radionuclide scan (technetium-99) is useful to identify bony lesions, inflammatory tumors, and stress fractures. Tumor vascularity can also be inferred from the flow phase and the blood pool images. Gallium or indium scans have high sensitivity for local infections. Thallium-201 chloride scintiscans have >90% sensitivity and between 80% and 90% accuracy in detecting malignant bone or soft-tissue tumors.

**Ultrasonography**

Ultrasonography is useful to evaluate suspected fluid-filled lesions such as popliteal cyst and hip joint effusions. Major indications for ultrasonography are fetal studies of the extremities and spine, including detection of congenital anomalies like spondylolisthesis, fractures suggesting osteogenesis imperfecta, developmental dysplasia of the hip, joint effusions, occult neonatal spinal dysraphism, foreign bodies in soft tissues, and popliteal cysts of the knee.

**Magnetic Resonance Imaging**

MRI is the imaging modality of choice for defining the exact anatomic extent of most musculoskeletal lesions (particularly if the structure is soft tissue). MRI avoids ionizing radiation and doing does not produce any known harmful effects. It produces excellent anatomic images of the musculoskeletal system, including the soft tissue, bone marrow cavity, spinal cord, and brain. It is especially useful for defining the extent of soft-tissue lesions, infections, and injuries. Tissue planes are well delineated, allowing more accurate assessment tumor invasion into adjacent structures. Cartilage structures can be visualized (articular cartilage of the knee can be distinguished from the fibrocartilage of the meniscus). MRI is also helpful in visualizing unossified joints in the pediatric population including the shoulders, elbows, and hips of young infants.
**Magnetic Resonance Angiography**
Magnetic resonance angiography has largely replaced routine angiography in the preoperative assessment of vascular lesions and bone tumors. Magnetic resonance angiography provides good visualization of peripheral vascular branches and tumor neovascularity in patients with primary bone tumors.

**Computed Tomography**
CT has enhanced the evaluation of multiple musculoskeletal disorders. Coronal, sagittal, and axial imaging is possible with CT including 3-dimensional reconstructions that can be beneficial in evaluating complex lesions of the axial and appendicular skeleton. It allows visualization of the detailed bone anatomy and the relationship of bones to contiguous structures. CT is useful to readily evaluate tarsal coalition, accessory navicular bone, infection, growth plate arrest, osteoid osteoma, pseudoarthrosis, bone and soft tissue tumors, spondylolysis, and spondylolisthesis. CT is superior to MRI for assessing bone involvement and cortical destruction (even subtle changes), including calcification or ossification and fracture (particularly if displacement of an articular fracture is suspected.

**LABORATORY STUDIES**
Laboratory tests are occasionally necessary in the evaluation of a child with musculoskeletal disorder. These may include a complete blood cell count; erythrocyte sedimentation rate; C-reactive protein assay; Lyme titers; and blood, wound, joint, periosteum, or bone cultures for infectious conditions such as septic arthritis or osteomyelitis. Rheumatoid factor, antinuclear antibodies, and human leukocyte antigen B27 may be necessary for children with suspected rheumatologic disorders. Creatine kinase, aldolase, aspartate aminotransferase, and dystrophin testing are indicated in children with suspected disorders of striated muscle such as Duchenne muscular dystrophy.

_Bibliography is available at Expert Consult._
Bibliography
Abnormalities affecting the osseous and articular structures of the foot may be congenital, developmental, neuromuscular, inflammatory, or acquired. Problems with the foot and/or toes may be associated with a host of connective tissue diseases and syndromes; overuse syndromes are commonly observed in young athletes. Symptoms may include pain and abnormal shoe wear; cosmetic concerns are common. The foot may be divided into the 

forefoot (toes and metatarsals), the midfoot (cuneiforms, navicular, cuboid), and the hindfoot (talus and calcaneus). While the tibiotalar joint (ankle) provides plantarflexion and dorsiflexion, the subtalar joint (between the talus and calcaneus) is oriented obliquely, providing inversion and eversion. Inversion represents a combination of plantarflexion and varus, while eversion involves dorsiflexion and valgus. The subtalar joint is especially important for walking on uneven surfaces. Inversion of the transverse tarsal (Chopart) joint locks the midfoot to provide a stable base on which to perform toe off during the gait cycle. Eversion of the transverse tarsal joint unlocks the hindfoot to provide accommodation during heel strike of the of the gait cycle. The talonavicular and calcaneocuboid joints connect the midfoot with the hindfoot.

674.1 Metatarsus Adductus  
Jennifer J. Winell and Richard S. Davidson

Metatarsus adductus involves adduction of the forefoot relative to the hindfoot. When the forefoot is supinated and adducted, the deformity is termed metatarsus varus (Fig. 674-1). The disorder is common in newborns, most frequently caused by intrauterine molding; the deformity is bilateral in 50% of cases. As with other intrauterine positional foot deformities, a careful hip and neck examination should always be performed to look for other abnormalities associated with intrauterine positioning.

CLINICAL MANIFESTATIONS
The forefoot is adducted (occasionally supinated), whereas the midfoot and hindfoot are normal. The lateral border of the foot is convex, and the base of the 5th metatarsal appears prominent. Range of motion at the ankle and subtalar joints is normal. Both the magnitude and the degree of flexibility should be documented. When the foot is viewed from the plantar surface, a line through the midpoint of (and parallel to) the heel should normally extend through the 2nd toe. Flexibility is assessed by stabilizing the hindfoot and midfoot in a neutral position with 1 hand and applying pressure over the 1st metatarsal head with the other. Correction with little pressure is indicative of a more flexible deformity. In the walking child with an uncorrected metatarsus adductus deformity, an in-toe gait and abnormal shoe wear may occur. A subset of patients will also have a dynamic adduction deformity of the great toe (hallux varus), which is often most noticeable during ambulation. This usually improves spontaneously and does not require treatment.

RADIOGRAPHIC EVALUATION
Radiographs are not performed routinely in infants. Older children with residual deformity should have anteroposterior (AP) and lateral weight-bearing or simulated weight-bearing radiographs. The AP radiographs demonstrate adduction of the metatarsals at the tarso-metatarsal articulation and an increased intermetatarsal angle between the 1st and 2nd metatarsals.

TREATMENT
The treatment of metatarsus adductus is based on the rigidity of the deformity; most children respond to nonoperative treatment. Deformities that are flexible and overcorrect into abduction with passive manipulation may be observed. Those feet that correct just to a neutral position may benefit from stretching exercises which can be demonstrated to the parents in the office. In a walking child, the parents can try reversing the shoes as well. If this is not effective, reverse-last shoes to maintain the abducted position of foot can be prescribed. These are worn full time (22 hr/day), and the condition is reevaluated in 4-6 wk.

Figure 674-1 Clinical picture of metatarsus adductus with a normal foot on opposite side.
If improvement occurs, treatment can be continued. If there is no improvement, serial plaster casts should be considered. When stretching a foot with metatarsus adductus, care should be taken to maintain the hindfoot in neutral to slight varus alignment to avoid creating hindfoot valgus. Feet that cannot be corrected to a neutral position may benefit from serial casting; the best results are obtained when treatment is started before 8 mo of age. In addition to stretching the soft tissues, the goal is to alter physeal growth and stimulate remodeling, resulting in permanent correction. Once flexibility and alignment are restored, orthoses or corrective shoes are generally recommended for an additional period. A dynamic hallux varus usually improves spontaneously, and no active treatment is required.

Surgical treatment may be considered in the small subset of patients with symptomatic residual deformities that have not responded to previous treatment. Surgery is generally delayed until children are 4-6 yr of age. Cosmesis is often a concern, and pain and/or the inability to wear certain types of shoes may occasionally lead patients to consider surgery. Options for surgical treatment include either soft-tissue releases or osteotomies. An osteotomy (midfoot or multiple metatarsals) is most likely to result in permanent restoration of alignment.

Bibliography is available at Expert Consult.

### 674.2 Calcaneovalgus Feet

Jennifer J. Winell and Richard S. Davidson

A common finding in the newborn, the calcaneovalgus foot is secondary to in utero positioning. Excessive dorsiflexion and eversion are observed in the hindfoot, and the forefoot may be abducted. There may be an associated external tibial torsion (see Chapter 675).

**CLINICAL MANIFESTATIONS**

The infant typically presents with the foot dorsiflexed and everted, and occasionally the dorsum of the foot or toes, will be in contact with the anterolateral surface of the lower leg (Fig. 674-2). Dimpling may be indicative of reduced subcutaneous fat at the dorsolateral ankle. Plantarflexion and inversion are often restricted. As with other intrauterine positional deformities, a careful hip examination should be performed; if there is any concern, hip ultrasonography should be considered. When comparing risk for developmental hip dysplasia (DDH) with other congenital foot deformities, congenital calcaneovalgus has the highest association with 19.4% of patients having coexisting DDH. The calcaneovalgus foot may be confused with a congenital vertical talus and may rarely be associated with a posteromedial bow of the tibia. A calcaneovalgus deformity may also be seen in older patients, typically those with a neuromuscular imbalance involving weakness or paralysis of the gastrocsoleus muscle (polio, myelomeningocele).

**RADIOGRAPHIC EVALUATION**

Radiographs are usually not required but should be ordered if the deformity fails to correct spontaneously or with early treatment. AP and lateral radiographs along with a lateral radiograph of the foot in maximal plantarflexion may help distinguish calcaneovalgus from a congenital vertical talus or congenital oblique talus. Evaluation of the position of the talus in relation to the navicular in both the lateral and maximally plantarflexed lateral view confirm congenital vertical talus. If a posteromedial bow of the tibia is suspected, AP and lateral radiographs of the tibia and fibula are necessary. In postero medial bowing of the tibia, the deformity is located in the tibia with the apex of deformity positioned posterior and medial. All three conditions may be confused clinically with calcaneovalgus feet.

**TREATMENT**

Mild cases of calcaneovalgus foot, in which full passive range of motion is present at birth, require no active treatment. These usually resolve within the 1st few wk of life. A gentle stretching program, focusing on plantarflexion and inversion, is recommended for cases with some restriction in motion. For cases with a greater restriction in mobility, serial casts may be considered to restore motion and alignment. Casting is rarely required in the treatment of calcaneovalgus feet. The management for those cases associated with a posteromedial bow of the tibia is similar.

Bibliography is available at Expert Consult.

### 674.3 Talipes Equinovarus (Clubfoot)

Jennifer J. Winell and Richard S. Davidson

Clubfoot or congenital talipes equinovarus (CTEV) is the term used to describe a deformity involving malalignment of the calcaneotalar-naviccular complex. Components of this deformity may be best understood using the mnemonic CAVE (cavus, adductus, varus, equinus). Although this is predominantly a hindfoot deformity, there are plantarflexion (cavus) of the first ray and adduction of the forefoot/midfoot on the hindfoot. The hindfoot is in varus and equinus. The clubfoot deformity may be positional, congenital, associated with a variety of underlying diagnoses (neuromuscular or syndromic) or a focal dysplasia of musculoskeletal tissue distal to the knee.

The **positional (or postural) clubfoot** is a normal foot that has been held in a deformed position in utero and is found to be flexible on examination in the newborn nursery. The **congenital clubfoot** can either be idiopathic or syndromic. There is a spectrum of severity, but clubfoot associated with neuromuscular diagnoses or syndromes is...
Bibliography

Bibliography


CLINICAL MANIFESTATIONS

A complete physical examination should be performed to rule out coexisting musculoskeletal and neuromuscular problems. The spine should be inspected for signs of occult dysraphism. Examination of the infant clubfoot demonstrates forefoot cavus and adductus and hindfoot varus and equinus (Fig. 674-3). The degree of flexibility varies, and all patients will exhibit calf atrophy. Internal tibial torsion, foot length shortening and leg-length discrepancy (shortening of the ipsilateral extremity) will be observed in a subset of cases. Although classically not associated with DDH (see Chapter 678), there is a higher association of CTEV and DDH than in the general population.

RADIOGRAPHIC EVALUATION

Anteroposterior and lateral radiographs are not recommended for idiopathic clubfoot. For arthrogrypotic or syndromic feet, x-rays may be helpful but must be performed, with the foot held in the maximally corrected position. Multiple radiographic measurements can be made to describe malalignment between the tarsal bones. The navicular bone does not ossify until 3-6 yr of age, so the focus of radiographic interpretation is the relationships between segments of the foot, forefoot to hindfoot. A common radiographic finding is "parallelism" between lines drawn through the axis of the talus and the calcaneus on the lateral radiograph, indicating hindfoot varus. X-ray may be particularly useful for older children with persistent or recurrent deformities that are difficult to assess.

TREATMENT

Nonoperative treatment is initiated in all infants and should be started as soon as possible following birth. Techniques have included taping and strapping, manipulation and serial casting, and functional treatment. Historically, a significant percentage of patients treated by manipulation and casting required a surgical release, which was usually performed between 3 and 12 mo of age. Although many feet remain well aligned after surgical releases, a significant percentage of patients have required additional surgery for recurrent or residual deformities. Stiffness remains a concern at long-term follow-up. While pain is uncommon in childhood and adolescence, symptoms may appear during adulthood. These concerns have led to considerable interest in less-invasive methods for treating the deformity. The Ponseti method of clubfoot treatment, which has now become the standard of initial treatment, involves a specific technique for manipulation and serial casting and may be best described as minimally invasive rather than nonoperative. The order of correction follows the mnemonic CAVE. Weekly cast changes are performed; 5-10 casts are typically required. The most difficult deformity to correct is the hindfoot equinus, and approximately 90% of patients will require a percutaneous tenotomy of the heel cord as an outpatient. Following the tenotomy, a long leg cast with the foot in maximal abduction (up to 70 degrees) and dorsiflexion is worn for 3-4 wk; the patient then begins a bracing program. An abduction brace is worn full time for 3 mo and then at nighttime for 3-5 yr. A small subset of patients (up to 20%) with recurrent, dynamic supination deformity will require transfer of the tibialis anterior tendon to the middle cuneiform for recurrence. Although most patients require some form of surgery, the procedures are minimal in comparison with extensive surgical release, which requires lengthening and/or release of muscles and tendons about the ankle and capsulotomy of the major joints to reposition the foot. The results of the Ponseti method are excellent at up to 40 yr of follow-up. Despite casting, children do not have much dysfunction or delay in achieving normal motor milestones. Compliance with the splinting program is essential; recurrence is common if the brace is not worn as recommended. Functional treatment, or the "French method," involves daily manipulations (supervised by a physical therapist) and splinting with elastic tape, as well as continuous passive motion (machine required) while the baby sleeps. While results are promising, it is usually performed in the
inpatient setting as the method is labor intensive. Implementation on an outpatient basis may be challenging, although just as successful. It remains unclear whether the technique will gain popularity in the United States. These minimally invasive methods are most successful when treatment is begun at birth or during the 1st few mo of life and with good compliance with postmanipulation bracing. As there are varying degrees of severity for idiopathic CTEV, grading systems have been proposed based on rigidity and magnitude of deformity. Aggressive surgical realignment has a definite role in the management of clubfeet, especially in the minority of congenital clubfeet that have failed nonoperative or minimally invasive methods, and for the rigid neuromuscular and syndromic clubfeet. In such cases, nonoperative methods such as the Ponseti technique may potentially be of value in decreasing the magnitude of surgery required. Common surgical approaches include a release of the involved joints (realignment of the tarsal bones), a lengthening of the shortened posteromedial musculotendinous units, and usually pinning of the foot in the corrected position. The “a la carte” method allows the surgeon to apply the principles to be tailored to the unique characteristics of each deformity. For older children with untreated clubfeet or those in whom a recurrence or residual deformity is observed, bony procedures (ostotomies) may be required in addition to soft-tissue surgery. Triple arthrodesis is reserved as salvage for painful, deformed feet in adolescents and adults.

Bibliography is available at Expert Consult.

674.4 Congenital Vertical Talus
Jennifer J. Winell and Richard S. Davidson

Congenital vertical talus is an uncommon foot deformity in which the midfoot is dorsally dislocated on the hindfoot and the ankle is in fixed equinus. There is nearly an even split between idiopathic cases and cases with an underlying neuromuscular condition or a syndrome. Neurologic causes include myelodysplasia, tethered cord, and sacral agenesis. Other associated conditions include arthrogryposis, Larsen syndrome, multiple pterygium syndrome, and chromosomal abnormalities (trisomy 13-15, 19; see Chapter 81). Depending on the age at diagnosis, the differential diagnosis may include a calcaneovalgus foot, oblique talus (talonavicular joint reduces passively), flexible flatfoot with a tight Achilles tendon, and tarsal coalition. Genetic studies are ongoing regarding abnormal muscle morphology on biopsy.

CLINICAL MANIFESTATIONS
Congenital vertical talus has also been described as a rocker-bottom foot (Fig. 674-4) or a Persian slipper foot. The plantar surface of the foot is convex, and the talar head is prominent along the medial border of the midfoot. The fore part of the foot is dorsiflexed (dorsally dislocated on the hindfoot) and abducted relative to the hindfoot, and the hindfoot is in equinus and valgus. There is an associated contracture of the anterolateral (tibialis anterior, toe extensors) and the posterior (Achilles tendon, peroneals) soft tissues. The deformity is typically rigid. A thorough physical examination is required to identify any coexisting neurologic and/or musculoskeletal abnormalities.

RADIOGRAPHIC EVALUATION
AP, lateral, and maximal plantarflexion and dorsiflexion lateral radiographs should be obtained when the diagnosis is suspected. The plantarflexion view helps to determine whether the dorsal subluxation or dislocation of the midfoot on the hindfoot can be reduced passively. The dorsiflexion lateral view confirms the equinus contracture of the ankle. Although the navicular does not ossify until 3-6 yr of age, the relationship between the talus and the 1st metatarsal may be evaluated.

TREATMENT
The initial management consists of serial manipulation and casting, which is started shortly after birth. A “reverse” Ponseti method of casting is particularly useful in stretching out the dorsiflexion and valgus deformities. Open reduction and pin fixation can then stabilize the midfoot allowing simultaneous heel cord tenotomy and dorsiflexion with casting to correct the ankle equinus.

In recalcitrant cases the competing deformities of the midfoot and the hindfoot make conservative treatment difficult. Initially, an attempt is made to reduce the dorsal dislocation of the forefoot/midfoot on the hindfoot. Once this has been achieved, attention can be directed toward stretching the hindfoot contracture. These deformities are typically rigid, and surgical intervention is required in the majority of cases. In such cases, casting helps to stretch out the contracted soft tissues. Surgery is generally performed between 6 and 12 mo of age; a soft-tissue release is performed as a 1 or 2 stage procedure. One component involves release/lengthening of the contracted anterior soft tissues in concert with an open reduction of the talonavicular joint, while the other involves a posterior release with lengthening of the contracted musculotendinous units. Fixation with Kirschner wires is commonly performed to maintain alignment. Postoperatively, casting is employed for a variable period of time; patients often require the use of an orthosis for extended periods, depending on the underlying diagnosis. Salvage options for recurrent or residual deformities in older children include a subtalar or triple arthrodesis.

Bibliography is available at Expert Consult.

674.5 Hypermobile Pes Planus
(Flexible Flatfeet)
Jennifer J. Winell and Richard S. Davidson

Flatfoot is a common diagnosis; it has been estimated that up to 23% of the public may be affected, depending on the diagnostic criteria. Three types of flatfeet may be identified: a flexible flatfoot, a flexible flatfoot with a tendo-Achilles contracture, and a rigid flatfoot. Flatfoot describes a change in foot shape, and there are several abnormalities in alignment between the tarsal bones. There is eversion of the subtalar complex. The hindfoot is aligned in valgus. There is midfoot sag at the naviculocuneiform and/or the talonavicular joints. The forefoot is abducted relative to the hindfoot, and the head of the talus is uncovered and prominent along the plantar and medial border of the midfoot/hindfoot. Although hypermobile or flexible pes planus represents a common source of concern for parents, these children are rarely symptomatic. Flatfeet are common in neonates and toddlers and are associated with physiologic ligamentous laxity. Improvement may be seen when the longitudinal arch develops between 5 and 10 yr of age. Flatfoot is less common in societies where shoes are not worn during infancy and childhood. In general, comfortable flexible-soled shoes are recommended for children. Flexible flatfeet persisting into adolescence and adulthood are usually associated with familial ligamentous laxity and can often be identified in other family members.

CLINICAL MANIFESTATIONS
Patients typically have a normal longitudinal arch when examined in a non–weightbearing position or standing on the toes, but the arch disappears when standing flat. The hindfoot collapses into valgus, and the midfoot sag becomes evident. Generalized ligamentous laxity is commonly observed. Range of motion should be assessed at both the subtalar and the ankle joints and will be normal in patients with a flexible flatfoot. When assessing range of motion at the ankle, the foot should always be inverted while testing dorsiflexion. If the foot is neutral or everted, spurious dorsiflexion may occur through the midfoot, masking a tendo-Achilles contracture. For older children with untreated clubfeet or those in whom a recurrence or residual deformity is observed, bony procedures (ostotomies) may be required in addition to soft-tissue surgery. Triple arthrodesis is reserved as salvage for painful, deformed feet in adolescents and adults.
**Bibliography**

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Bibliography
Routine radiographs of asymptomatic flexible flatfeet are usually not indicated. If obtained for diagnostic reasons, weightbearing radiographs (AP and lateral) are required to assess the deformity. On the AP radiograph, there is widening of the angle between the longitudinal axis of the talus and the calcaneus, indicating excessive heel valgus. The lateral view shows distortion of the normal straight-line relationship between the long axis of the talus and the 1st metatarsal with sag either of the talonavicular or naviculocuneiform joint, resulting in flattening of the normal medial longitudinal arch (Fig. 674-5).

**TREATMENT**

Although the natural history of the flexible flatfoot remains unknown, there is little evidence to suggest that this condition results in long-term problems or disability. As such, treatment is reserved for the small
subset of patients who develop symptoms. Patients may complain of hindfoot pain, abnormal shoe wear or fatigue after long walking. These patients may benefit from a nonprescription orthosis, such as a medial arch support. Severe cases, often associated with an underlying connective tissue disorder such as Ehlers-Danlos syndrome (see Chapter 659) or Down syndrome (see Chapter 81), may benefit from a custom orthosis such as the UCBL (University of California Biomechanics Laboratory) orthosis to better control the hindfoot and prevent collapse of the arch. Although an orthosis may relieve symptoms, there is no evidence to suggest any permanent change in the shape of the foot or alignment of the tarsal bones. Patients with a flexible flatfoot and a tight tendo-Achilles should be treated with stretching exercises. Many times patients are referred to physical therapy to ensure that the patients are stretching appropriately. On occasion, the muscle will need to be lengthened surgically. For the few patients with persistent pain, surgical treatment can be considered. There has been considerable interest in a lateral column lengthening, which addresses all components of the deformity. The procedure involves an osteotomy of the calcaneus, with placement of a trapezoidal bone graft. A lengthening of the tendo-Achilles is required, often with a plantarflexion osteotomy of the medial cuneiform. This procedure preserves the mobility of the hindfoot joints, in contrast to a subtalar or triple arthrodesis. While a hindfoot arthrodesis may correct the deformity adequately, the stress transfer to neighboring joints may result in late-onset, painful degenerative changes.

**Bibliography is available at Expert Consult.**

### 674.6 Tarsal Coalition

Jennifer J. Winell and Richard S. Davidson

Tarsal coalition, also known as peroneal spastic flatfoot, is characterized by a painful, rigid flatfoot deformity and peroneal (lateral calf) muscle spasm but without true spasticity. It represents a congenital fusion or failure of segmentation between 2 or more tarsal bones. Any condition that alters the normal gliding and rotatory motion of the subtalar joint may produce the clinical appearance of a tarsal coalition. Thus, congenital malformations, arthritis or inflammatory disorders, infection, neoplasms, and trauma can be possible causes.

The most common tarsal coalitions occur at the medial talocalcaneal (subtalar) facet and between the calcaneus and navicular (calcaneonavicular). Coalitions can be fibrous, cartilaginous, or osseous. Tarsal coalition occurs in approximately 1% of the general population and appears to be inherited as an autosomal dominant trait with nearly full penetrance. Approximately 60% of calcaneonavicular and 50% of the medial facet talocalcaneal coalitions are bilateral.

**CLINICAL MANIFESTATIONS**

Approximately 25% of patients will become symptomatic, typically during the 2nd decade of life. Although the flatfoot and a decrease in subtalar motion may have been present since early childhood, the onset of symptoms may correlate with the additional restriction in motion that occurs as a cartilaginous bar ossifies. Recurrent “ankle sprains” often accompany the presenting symptoms. The timing of ossification varies between the talonavicular (3-5 yr of age), the calcaneonavicular (8-12 yr of age), and the talocalcaneal (12-16 yr of age) coalitions. Hindfoot pain is commonly observed, especially in the region of the sinus tarsi and also under the head of the talus. Symptoms are activity related and are often increased with running or prolonged walking, especially on uneven surfaces. There may be tenderness over the site of the coalition and/or pain with testing of subtalar motion. The clinical appearance of a flatfoot is seen in both the weightbearing and non-weightbearing positions. There is a restriction in subtalar motion.

**RADIOGRAPHIC EVALUATION**

AP and lateral weightbearing radiographs and an oblique radiograph of the foot should be obtained (Table 674-1). A calcaneonavicular coalition is seen best on the oblique radiograph (Fig. 674-6). On the lateral radiograph, there may be elongation of the anterior process of the calcaneus, known as the “anteater sign.” A talocalcaneal coalition may be seen on a Harris (axial) view of the heel. On the lateral radiograph, there may be narrowing of the posterior facet of the subtalar joint, or a C-shaped line along the medial outline of the talus and the inferior outline of the sustentaculum tali (“C sign”). This “C sign” is made up of the sustentaculum tali of the calcaneus in continuity with the coalition. Beaking of the anterior aspect of the talus on the lateral view is seen with some frequency, and results from an alteration in the distribution of stress. This finding does not imply the presence of degenerative arthritis. Irregularity in the subchondral bony surfaces may be seen in patients with a cartilaginous coalition, in contrast to a well-formed bony bridge in those with an osseous coalition. A fibrous coalition may require additional imaging studies to diagnose. While plain films may be diagnostic, a CT scan is the imaging modality of choice when a coalition is suspected (Fig. 674-7). In addition to securing the diagnosis, this study helps to define the degree of joint involvement in patients with a talocalcaneal coalition. Although uncommon, more than one tarsal coalition may be observed in the same patient. Only in young children, MRI may be more effective in identifying either the coalition or a differential diagnosis for the foot pain. MRI offers less radiation exposure but requires more time and may necessitate sedation.

**TREATMENT**

The treatment of symptomatic tarsal coalitions varies according to the type and extent of coalition, the age of the patient, and the presence and magnitude of symptoms. Treatment is required only for symptomatic coalitions, and the initial management consists of activity

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**Table 674-1** Radiographic Secondary Signs Associated with Tarsal Conditions

<table>
<thead>
<tr>
<th>Sign</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talar breaking</td>
<td>Posterior subtalar facet narrowing</td>
</tr>
<tr>
<td>Rounding and flattening of the lateral talus facet</td>
<td>Hypoplasia of the talus, shortening of the talar neck</td>
</tr>
<tr>
<td>Anterior nose sign</td>
<td>Ball-and-socket ankle joint</td>
</tr>
<tr>
<td>Continuous C-sign</td>
<td>Flatfoot deformity</td>
</tr>
<tr>
<td>Dyshoric sustentaculum tali (enlarged and ovoid on lateral radiograph)</td>
<td>Altered navicular morphology (wide or laterally tapering)</td>
</tr>
</tbody>
</table>


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**Figure 674-6** Oblique radiograph of the foot demonstrating a calcaneonavicular tarsal coalition.
Bibliography


restriction and nonsteroidal antiinflammatory medications, with or without a shoe insert. Immobilization in a short leg walking cast for 4-6 wk may be required in patients with more pronounced symptoms.

For patients with chronic pain despite an adequate trial of nonoperative therapy, surgical treatment should be considered, and options include resection of the coalition, osteotomy, or arthrodesis. For the calcaneonavicular coalition, resection and interposition of the extensor digitorum brevis muscle have been successful. Often, concomitant hindfoot valgus and contracture of the gastrocnemius-soleus is present. In these patients, more reliable pain relief can be obtained with resection of the coalition, correction of the hindfoot valgus by calcaneal lengthening osteotomy with bank bone graft and lengthening of the gastrocnemius-soleus. For those with extensive involvement of the joint and/or degenerative changes, a triple arthrodesis may be the best option; however, this is rarely needed in adolescents.

Bibliography is available at Expert Consult.

674.7 Cavus Feet

Jennifer J. Winell and Richard S. Davidson

Cavus is a deformity involving plantarflexion of the forefoot or midfoot on the hindfoot and may involve the entire forepart of the foot or just the medial column. The result is an elevation of the medial longitudinal arch (Fig. 674-8). A deformity of the hindfoot will often develop to compensate for the primary forefoot abnormality. While familial cavus may occur, the majority of patients with this deformity will have an underlying neuromuscular etiology. The initial goal is to rule out (and treat) any underlying causes. These diagnoses may relate to abnormalities of the spinal cord (occult dysraphism, tethered cord, polio, myelodysplasia, etc.) and peripheral nerves (hereditary motor and sensory neuropathies [see Chapter 613] such as Charcot-Marie-Tooth [CMT] disease, Dejerine-Sottas disease, or Refsum disease). Although a unilateral cavus foot is most likely to result from an occult intraspinal anomaly, bilateral involvement usually suggests an underlying nerve or muscle disease. Cavus is commonly observed in association with a hindfoot deformity. Two-thirds of CMT patients have pes cavovarus, while 80% of pes cavovarous is most commonly seen in patients with the hereditary motor and sensory neuropathies (CMT), with 80% of CMT patients having pes cavovarus and 65% of patients with cavovarous having CMT. In patients with hereditary motor and sensory neuropathies, progressive weakness and muscle imbalance result in plantarflexion of the 1st ray/medial column. To obtain a plantigrade foot, the hindfoot must roll into varus. With equinocavus, the hindfoot is in equinus, whereas in calcaneocavus (usually seen in polio or myelodysplasia), the hindfoot is in calcaneeus (excessive dorsiflexion).

674.8 Osteochondroses/Apophysitis

Jennifer J. Winell and Richard S. Davidson

Osteochondroses are idiopathic avascular necrosis of bones which may involve tarsal bones as well. Although rare, they may be observed in the tarsal navicular (Köhler disease) or the 2nd or 3rd metatarsal head (Freiberg infraction) (Fig. 674-9). These are generally self-limited conditions that commonly result in activity-related pain, which can at times be disabling. The treatment is based on the degree of symptoms and commonly includes restriction of activity. The diagnosis is often made by history and physical exam in conjunction with concordant radiographic findings. The navicular is particularly sensitive...
Bibliography
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as it is the last tarsal bone to ossify which may lead to compression from adjacent ossified bones. For patients with Köhler disease, non-surgical treatment with a short leg cast for 6-8 wk may provide significant relief. Patients with Freiberg infraction may benefit from a period of casting and/or shoe modifications such as a rocker-bottom sole, a stiff-soled shoe, or a metatarsal bar. Degenerative changes and collapse of the metatarsal head will occasionally occur following the gradual healing process, and surgical intervention is required in a small subset of cases. Procedures have included joint debridement, bone grafting, redirection osteotomy, subtotal or complete excision of the metatarsal head, and joint replacement.

Apophysitis represents inflammation at the tendinous insertion of a muscle from repetitive tensile loading and is most commonly observed during periods of rapid growth. These stresses result in microfractures at the fibrocartilaginous insertion site, associated with inflammation. Calcaneal apophysitis (Sever disease) is the most common cause of heel pain in children; treatment includes activity modification, nonsteroidal antiinflammatory medications, heel cord stretching exercises, and heel cushions or arch supports. Iselin disease represents an apophysitis at the 5th metatarsal base where the peroneus brevis attaches and is less common. Even though the mandate for imaging heel pain in all children remains controversial, radiographs should be considered when the symptoms are unilateral or with a failure to respond to treatment. A period of rest (6-8 wk) and avoidance of sports will often resolve symptoms, although recurrence is common until maturity when the apophyses close.

Bibliography is available at Expert Consult.

674.10 Toe Deformities
Jennifer J. Winell and Richard S. Davidson

JUVENILE HALLUX VALGUS (BUNION)
Juvenile hallux valgus is most common in females (~10-fold), and while a family history is uncommon, it is typically associated with familial ligamentous laxity. The etiology is multifactorial, and important factors include genetic factors, ligamentous laxity, pes planus, wearing shoes with a narrow toe box, and occasionally spasticity (cerebral palsy).

Clinical Manifestations
There is prominence of the 1st metatarsal head (MTP) joint and often erythema and callus from chronic irritation. The great toe is in valgus and is usually pronated, and there is splaying of the forefoot.Pes planus, with or without an associated heel cord contracture, is also observed commonly. Although cosmesis is perhaps the most common concern, patients may have pain in the region of the 1st MTP joint and/or difficulty with shoe wear.

Radiographic Evaluation
Weightbearing AP and lateral radiographs of the feet are obtained. On the AP view, common measurements include the angular relationships between the 1st and 2nd metatarsals (intermetatarsal angle, <10 degrees is normal) and between the 1st metatarsal and the proximal phalanx (hallux valgus angle, <25 degrees is normal). The orientation of the 1st metatarsal-medial cuneiform joint is also documented. On the lateral radiograph, the angular relationship between the talus and the 1st metatarsal helps to identify a midfoot break associated with pes planus. Radiographs are more helpful in surgical planning than in establishing the diagnosis.
Bibliography
Bibliography

Treatment

Conservative management of adolescent bunions consists primarily of shoe modifications. It is important that footwear accommodate the width of the forefoot. Patients should avoid wearing shoes with a narrow toe box and/or a high heel. Shoe modifications, such as a soft upper, bunion last, or heel cup, may also be recommended. In the presence of a pes planus, an orthotic to restore the medial longitudinal arch may be beneficial. If a teno-Achilles contracture is present, stretching exercises are recommended. The value of night splinting remains to be determined. Surgical treatment is reserved for those patients with persistent and disabling pain who have failed a course of nonoperative therapy. Surgery is not advised purely for cosmesis. Surgery is usually delayed until skeletal maturity to decrease the risk of recurrence or overcorrection. Radiographs are essential in preoperative planning to assess both the magnitude of deformity (hallux valgus angle, intermetatarsal angle, distal metatarsal articular angle) and associated features such as obliquity of the 1st metatarsal–medial cuneiform joint. Surgical treatment often involves a soft-tissue release and/or rebalancing procedure at the 1st MTP joint, and a single or double osteotomy of the 1st metatarsal to decrease foot width and realign the joints along the medial column of the forefoot. An arthrodesis of the 1st MTP joint may be indicated in patients with spasticity to prevent recurrence.

CURLY TOES

A curly toe is caused by contracture of the flexor digitorum longus, and there is flexion at the MTP and the interphalangeal (IP) joints associated with medial deviation of the toe. The toe usually lies underneath its neighbor, and the 4th and 5th toes are most commonly involved. The deformity rarely causes symptoms, and active treatment (stretching, splinting, or taping) is not required. Most cases improve over time, and a subset will resolve completely. For the rare case in which there is chronic pain or skin irritation, release of the flexor digitorum longus muscle at the distal IP joint may be considered when the child is older.

OVERLAPPING FIFTH TOE

Congenital digitus minimus varus, or varus 5th toe, involves dorsiflexion and adduction of the 5th toe. The 5th toe typically overlaps the 4th. There is also a rotatory deformity of the toe, and the nail tends to point outward. The deformity is usually bilateral and may have a genetic basis. Symptoms are frequent and involve pain over the dorsum of the toe from shoe wear. Nonoperative treatment has not been successful. For symptomatic patients, several different options for reconstruction have been described. Common features include releasing the contracted extensor tendon and the MTP joint capsule (dorsal, dorsomedial, or complete). A partial removal of the proximal phalanx and creation of a syndactyly between the 4th and 5th toes has been performed in conjunction with the release as well.

POLYDACTYLY

Polydactyly is the most common congenital toe deformity and is seen in approximately 2 in 1,000 births and is bilateral in 50% of cases. Polydactyly may be preaxial (great toe) or postaxial (5th toe), and occasionally one of the central toes is duplicated. Associated anomalies are found in approximately 10% of the preaxial and 20% of postaxial polydactyly. One-third of patients will also have polydactyly of the hand. Conditions that may be associated with polydactyly include Ellis-Van Creveld (chondroectodermal dysplasia), longitudinal deficiency of the tibia, and Down syndrome. The extra digit may be either rudimentary or well formed, and plain radiographs of the foot help to define the anatomy and evaluate any coexisting bony anomalies. Treatment is indicated for cosmesis and to allow for fitting with standard shoes. This involves surgical removal of the extra digit, and the procedure is generally performed between 9 and 12 mo of age. Rudimentary digits may be surgically excised earlier, but should not be “tied off.”

SYNDACTYLY

Syndactyly involves webbing of the toes, which may be incomplete or complete (extends to the tip of the toes), and the toenails may be confluent. There is often a positive family history, and the 3rd and 4th toes are involved most commonly. Symptoms are extremely rare, and cosmetic concerns are infrequent. Treatment is only required for a subset of cases in which there is an associated polydactyly (Fig. 674-10). In such cases, the border digit is excised, and the extra skin facilitates coverage of the wound. If the syndactyly does not involve the extra toe, then it can be observed. A complex syndactyly may be seen in patients with Apert syndrome.

HAMMER TOE

A hammer toe involves flexion at the proximal IP (PIP) joint with or without the distal IP (DIP) joint, and the MTP joint may be hyperextended. This deformity may be distinguished from a curly toe by the absence of rotation. The 2nd toe is most commonly involved, and a painful callus may develop over the dorsum of the toe where it rubs on the shoe. Nonoperative therapy is rarely successful, and surgery is recommended for symptomatic cases. A release of the flexor tendons will suffice in the majority of cases. Some authors recommend a transfer of the flexor tendon to the extensor tendon. For severe cases with significant rigidity, especially in older patients, a partial or complete resection of the proximal phalanx and a PIP fusion may be required.

MALLET TOE

Mallet toe involves a flexion contracture at the DIP joint and results from congenital shortening of the flexor digitorum longus tendon. Patients may develop a painful callus on the plantar surface of the tuft. As nonoperative therapy is usually unsuccessful, surgery is required for patients with chronic symptoms. For flexible deformities in younger children, release of the flexor digitorum longus tendon is recommended. For stiffer deformities in older patients, resection of the head of the middle phalanx, or arthrodesis of the DIP joint, may be considered.

CLAW TOE

A claw toe deformity involves hyperextension at the MTP joint and flexion at both the PIP and DIP joints, often associated with dorsal subluxation of the MTP joint. The majority are associated with an underlying neurologic disorder such as CMT disease. The etiology is usually muscle imbalance, and the extensor tendons are recruited to substitute for weakening of the tibialis anterior muscle. If treatment is elected, then surgery is required. Transfer of the extensor digitorum (or hallucis) tendon to the metatarsal neck is commonly performed along with a dorsal capsulotomy of the MTP joint and fusion of the PIP joint (IP joint of the great toe).

ANNULAR BANDS

Bands of amniotic tissue associated with amniotic disruption syndrome (early amniotic rupture sequence, congenital constriction band syndrome, annular band syndrome) may become entwined along the...
debunking may be required. Patients may elect to have an amputation if the process cannot be controlled by less extensive procedures.

**SUBUNGUAL EXOSTOSIS**

A subungual exostosis is a mass of normal bone tissue that projects out from the dorsal and medial surface of a toe, under the nail. The etiology is unknown but may relate to minor, repetitive trauma. The great toe is involved most often. Patients present with discomfort, and the toenail may be elevated. The lesion may be demonstrated on plain radiographs, and histologically involves normal bone with a fibrocartilaginous cap. The treatment for symptomatic lesions is excision, and the recurrence rate is in the range of 10%.

**INGROWN TOENAIL**

Ingrown toenails are relatively common in infants and young children and usually involve the medial or lateral border of the great toe. Symptoms include chronic irritation and discomfort, and recurrent infection is seen in some cases. Parents should be instructed when cutting toe nails to cut straight across the distal aspect of the nail, rather than curve inwards at the nail edges. If conservative measures including shoe modifications, warm soaks, and appropriate nail trimming fail to control the symptoms, then surgical removal of a portion of the nail should be considered.

**Bibliography is available at Expert Consult.**

### 674.11 Painful Foot

*Jennifer J. Winell and Richard S. Davidson*

Table 674-2 shows a differential diagnosis for foot pain in different age ranges. In addition to the history and physical examination, plain extremities, resulting in a spectrum of problems from in utero amputation (Fig. 674-11) to a constriction ring along a digit (Fig. 674-12) (see Chapter 108). These rings, if deep enough, may result in impairment of arterial or venous blood flow. Even though concerns regarding tissue viability are less common, swelling from impairment in venous return is often a great problem. The treatment of annular bands usually involves observation; however, circumferential release of the band may be required emergently if arterial inflow is obstructed or electively to relieve venous congestion.

**MACRODACTYLY**

Macrodactyly represents an enlargement of the toes and may occur as an isolated problem or in association with a variety of other conditions such as Proteus syndrome (Fig. 674-13), neurofibromatosis, tuberous sclerosis, and Klippel-Trenaunay-Weber syndrome. This condition results from a deregulation of growth, and there is hyperplasia of one or more of the underlying tissues (osseous, nervous, lymphatic, vascular, fibrofatty). Macrodactyly of the toes may be seen in isolation (localized gigantism) or with enlargement of the entire foot. In addition to cosmetic concerns, patients may have difficulty wearing standard shoes. The treatment is observation, if possible. This is a difficult condition to treat surgically, and complications are frequent. For involvement of a single toe, the best option may be a resection of the ray (including the metatarsal). For greater degrees of involvement, debunking of the various tissues is required. Often, a growth arrest of the underlying osseous structures is performed. Stiffness and wound problems are common. The rate of recurrence is high, and more than one figure 674-11 constriction band syndrome with congenital amputation.

Figure 674-12 Constriction band syndrome with foot involvement.

Figure 674-13 Macroducty of the great toe in a case of Proteus syndrome.
Bibliography

radiographs are most helpful in establishing the diagnosis. Occasionally, more sophisticated imaging modalities such as CT or MRI will be required.

**674.12 Shoes**

*Jennifer J. Winell and Richard S. Davidson*

In toddlers and children, a well-fitting shoe with a flexible sole is recommended. This recommendation is in part based on studies suggesting that the development of the longitudinal arch seems to be best in societies where shoes are not worn and flatfeet are more common in shod children. Well-cushioned, shock-absorbing shoes are helpful in the child and adolescent athlete to decrease the chances of developing an overuse injury. Otherwise, shoe modifications are generally reserved for abnormalities in either alignment between segments of the foot or symptoms from an underlying condition (such as a limb-length discrepancy). Numerous modifications are available.

As a rule, shoes protect the foot from abnormal temperature as well as rough surfaces and sharp objects but have not been shown to help the normal foot develop. Poorly fitting shoes may create problems.

*Bibliography is available at Expert Consult.*
Bibliography

During the 7th wk of intrauterine life, the lower limb rotates medially to bring the great toe toward the midline. The hip joint forms by the 11th wk; the proximal femur and acetabulum continue to develop until physeal closure in adolescence. At birth, the femoral neck is rotated forward approximately 40 degrees. This forward rotation is referred to as anteversion (the angle between the axis of the femoral neck and the transcondylar axis). The increased anteversion increases the internal rotation of the hip. Femoral anteversion decreases to 15-20 degrees by 8-10 yr of age. Conditions such as cerebral palsy that involve spasticity of the lower extremities can result in the persistence of fetal anteversion, which results in torsional abnormalities of the lower limb and gait disturbances. The second source of limb rotation is found in the tibia. Infants can have 30 degrees of medial rotation of the tibia, and by maturity the rotation is between 5 degrees of medial rotation and 15 degrees of lateral rotation (Fig. 675-1). Excessive medial rotation of tibia is referred to as medial tibial torsion. This is very common, and although very concerning to parents, very rarely requires treatment. Observation is indicated for most cases of medial tibial torsion. The tibial torsion is the angular difference between the axis of the knee and the transmalleolar axis. The medial or lateral rotation beyond ±2 SDs from the mean is considered abnormal rotation. The third source of rotational (axial) abnormalities of the lower extremity comes from the foot. Metatarsus adductus can cause the toes to point inward, and can be assessed by assessing if the medial border of the foot is straight.

Torsional deformity may be simple, involving a single segment, or complex, involving multiple segments. Complex deformities may be additive (internal tibial torsion and internal femoral torsion are additive) or compensatory (external tibial torsion and internal femoral torsion are compensatory).

The normal tibiofemoral angle at birth is 10-15 degrees of physiologic varus. The alignment changes to 0 degrees by 18 mo, and physiologic valgus up to 12 degrees is reached in between 3 and 4 yr of age. The normal valgus of 7 degrees is achieved by 5-8 yr of age (Fig. 675-2). Persistence of varus beyond 2 yr of age may be pathologic and is seen in conditions such as Blount disease. Overall, 95% of developmental physiologic genu varum and genu valgum cases resolve with growth. Persistent genu valgum or valgus into adolescence is considered pathologic and deserves further evaluation.

Bibliography is available at Expert Consult.

675.2 Evaluation

Keith D. Baldwin and Lawrence Wells

In evaluation of concerns relating to the limb, the pediatrician should obtain a history of the onset, progression, functional limitations, previous treatment, evidence of neuromuscular disorder, and any significant family history.

The examination should assess the exact torsional profile and include (1) foot progression angle, (2) femoral anteversion, (3) tibial version with thigh–foot angle, and (4) assessment of foot adduction and abduction.

FOOT PROGRESSION ANGLE

Limb position during gait is expressed as the foot progression angle and represents the angular difference between the axis of the foot with the direction in which the child is walking. Its value is usually estimated by asking the child to walk in the clinic hallway (Fig. 675-3). Inward rotation of the foot is assigned a negative value, and outward rotation is designated with positive value. The normal foot progression angle in children and adolescents is 10 degrees (range: −3 to 20 degrees). The foot progression angle serves only to define whether there is an in-toeing or out-toeing gait.

FEMORAL ANTEVERSION

Measuring the hip rotation with the child in prone position, the hip in neutral flexion or extension, thighs together, and the knees flexed 90
Bibliography


Figure 675-1 A-F, The rotational profile from birth to maturity is depicted graphically. All graphs include 2 SD from the mean for the foot progression angle (FPA) for femoral medial rotation (MR) and lateral rotation (LR) (for boys and girls), and the thigh–foot angle (TFA). (From Morrissey RT, Weinstein SL, editors: Lovell and Winter’s pediatric orthopaedics, ed 3, Philadelphia, 1990, Lippincott Williams & Wilkins.)

Figure 675-2 The normal coronal alignment of the knee plotted for age. (From Salenius P, Vanka E: The development of the tibiofemoral angle in children. J Bone Joint Surg Am 57:259–261, 1975.)
degrees indirectly assesses the anteversion (Fig. 675-4). Both hips are assessed at the same time. As the lower leg is rotated ipsilaterally, this produces internal rotation of the hip, whereas contralateral rotation produces external rotation. Excessive anteversion increases internal rotation, and, retroversion increases the external rotation. The amount of anteversion can be roughly estimated by palpating the greater trochanter of the hip while internally rotating the limb. The point of maximal prominence of the greater trochanter corresponds to femoral anteversion.

TIBIAL ROTATION

Tibial rotation is measured using the transmalleolar angle. The transmalleolar angle is the angle between the longitudinal axis of the thigh with a line perpendicular to the axis of the medial and lateral malleolus (Fig. 675-5). In the absence of foot deformity, the thigh–foot angle is preferred (Fig. 675-6). It is measured with the child lying prone. The angle is formed between the longitudinal axis of the thigh and the longitudinal axis of the foot. It measures the tibial and hindfoot rotational status. Inward rotation is assigned a negative value, and outward rotation is designated a positive value. Inward rotation indicates internal tibial torsion, whereas outward rotation represents external tibial torsion. Infants have a mean angle of −5 degrees (range: −35 to 40 degrees) as a consequence of normal in utero position. In midchildhood through adult life, the mean thigh–foot angle is 10 degrees (range: −5 to 30 degrees).
INTERNAL FEMORAL TORSION

Medial (internal) tibial torsion manifests with in-toeing gait and is commonly associated with congenital metatarsus varus, genu valgum, or femoral anteversion. This condition is usually seen during the 2nd yr of life. Normally at birth, the medial malleolus lies behind the lateral malleolus, but by adulthood, it is reversed, with the tibia in 15 degrees of external rotation. The treatment is essentially observation and reassurance, because spontaneous resolution with normal growth and development can be anticipated. Significant improvement usually does not occur until the child begins to pull to stand and walk independently. Thereafter, correction can be seen as early as 4 yr of age and in some children by 8-10 yr of age. Persistent deformity with functional impairment is treated with supramalleolar osteotomy, which is rarely necessary.

EXTERNAL FEMORAL TORSION

External femoral torsion can follow a slipped capital femoral epiphysis; there is a low threshold to perform radiographs of the hips in children older than 10 yr of age. Femoral retrotorsion, when of idiopathic origin, is usually bilateral. The disorder is associated with an out-toeing gait and increased incidence of degenerative arthritis. The clinical examination of external femoral torsion shows excessive hip external rotation and limitation of internal rotation. The hip will externally rotate up to 70-90 degrees, whereas internal rotation is only 0-20 degrees. If slipped capital femoral epiphysis is detected, it is treated surgically. Occasionally, persistent femoral retroversion after slipped capital femoral epiphysis can produce functional impairment such as a severe out-toeing gait and difficulty opposing one’s knees in the sitting position. The latter can be disabling to adolescent girls. Should this occur, a Southwick osteotomy or surgical realignment might be necessary.

EXTERNAL TIBIAL TORSION

Lateral tibial torsion is less common than medial rotation and is often associated with a calcaneovalgus foot. It can be compensatory to persistent femoral anteverision and idiopathic or secondary to a tight iliotibial band. The natural growth rotates the tibia externally, and hence external tibial torsion can become worse with time. Clinically, the patella faces outward when the foot is straight. The thigh–foot angle and the transmalleolar angle are increased. There may be associated patellofemoral instability with knee pain. Though some correction can occur with growth, extremely symptomatic children need supramalleolar osteotomy, which is usually done by 10-12 yr of age.

METATARSUS ADDUCTUS

Metatarsus adductus (see Chapter 674.1) manifests with forefoot adduction and inversion of all metatarsals. Ten percent to 15% are associated with hip dysplasia. The prognosis is good, because the majority get better with nonoperative intervention. The feet, which are flexible and correctable up to neutral, are treated with stretching exercises. Those that are not completely correctable are treated with serial casting. Rigid deformities, which are not correctable by stretching, are treated with medial capsulotomy of the 1st metatarsal cuneiform joint and soft-tissue release by 2 yr of age. Osteotomies of the base of the metatarsal may be performed after 6 yr of age.

Foot Shape and Position

The foot is observed for any deformities in prone and standing position. The heel bisector line (HBL) is used to evaluate the foot adduction and abduction deformities. The HBL is a line that divides the heel in 2 equal halves along the longitudinal axis (Fig. 675-7). It normally extends to the 2nd toe. When the HBL points medial to the 2nd toe, the forefoot is abducted, and when the HBL is lateral to the 2nd toe, the forefoot is adducted. Other lower-extremity problems, such as heel varus or valgus, can also make assessment of axial plane issues more difficult.

It is also important to screen every affected child for associated hip dysplasia and neuromuscular problems (cerebral palsy).

Bibliography is available at Expert Consult.

675.3 Torsional Deformities

Keith D. Baldwin and Lawrence Wells

INTERNAL FEMORAL TORSION

In-toeing gait most commonly results from excessive femoral anteverision. It occurs more commonly in girls than boys (2:1) in children 3-6 yr of age. The etiology of femoral torsion is controversial. Some believe that it is congenital and a result of persistent infantile femoral anteverision, whereas others believe it is acquired secondary to abnormal sitting habits. Some children are in habit of sitting in a W position or sleeping prone. On examination, most children with this condition have generalized ligamentous laxity. Gait examination reveals that entire leg is inwardly rotated. Internal hip rotation is increased beyond 70 degrees, and consequently the external rotation is restricted to 10-20 degrees. The patellae are pointing inward when the foot is straight, and compensatory external rotation of the tibia is demonstrated. The amount of anteverision can be roughly estimated by palpating the greater trochanter of the hip while internally rotating the limb. The point of maximal prominence of the greater trochanter corresponds to femoral anteverision.

Diagnosis is made clinically on examination; CT can provide objective measurements but is rarely indicated. The treatment is predominantly observation and correction of abnormal sitting habits. The torsion usually corrects with growth by 8-10 yr of age. Persistent deformity, unacceptable cosmesis, functional impairment, anteverversion >45 degrees, and no external rotation beyond neutral are some of the indications for operative intervention. Surgery involves derotation osteotomy of the femur but is rarely performed or necessary.

FOOT SHAPE AND POSITION

The foot is observed for any deformities in prone and standing position. The heel bisector line (HBL) is used to evaluate the foot adduction and abduction deformities. The HBL is a line that divides the heel in 2 equal halves along the longitudinal axis (Fig. 675-7). It normally extends to the 2nd toe. When the HBL points medial to the 2nd toe, the forefoot is abducted, and when the HBL is lateral to the 2nd toe, the forefoot is adducted. Other lower-extremity problems, such as heel varus or valgus, can also make assessment of axial plane issues more difficult.

It is also important to screen every affected child for associated hip dysplasia and neuromuscular problems (cerebral palsy).

Bibliography is available at Expert Consult.

675.4 Coronal Plane Deformities

Keith D. Baldwin and Lawrence Wells

Genu varum and genu valgum are common pediatric deformities of the knee. Figure 675-2 presents the age-appropriate normal values for
Bibliography


Bibliography
knee angle. Tibial bowing is common during the 1st yr, bowlegs are common during the 2nd yr, and knock-knees are most prominent between 3 and 4 yr of age.

GENU VARUM

Physiologic bowleg is a common torsional combination that is secondary to normal in utero positioning (Fig. 675-8). Spontaneous resolution with normal growth and development can be anticipated. Persistence of varus beyond 2 yr of age may be pathologic. The different causes are metabolic bone disease (vitamin D deficiency, rickets, hypophosphatasia), asymmetric growth arrest (trauma, infection, tumor, Blount), bone dysplasia (dwarfism, metaphyseal dysplasia), and congenital and neuromuscular disorders (Table 675-1). It is prudent to differentiate physiologic bowing from Blount disease (Table 675-2). Physiologic bowing should also be differentiated from rickets and skeletal dysplasia. Rickets has classic bone changes with trumpeting widening and fraying of the metaphysis and widening of the physis (see Chapter 51).

TIBIA VARA

Idiopathic tibia vara, or Blount disease, is a developmental deformity resulting from abnormal endochondral ossification of the medial aspect of the proximal tibial physis leading to varus angulation and medial rotation of the tibia (Fig. 675-9). The incidence is greater in African-Americans and in toddlers who are overweight, have an affected family member, or started walking early in life. It has been classified into 3 types, depending on the age at onset: infantile (1-3 yr of age), juvenile (4-10 yr of age), and adolescent (11 yr or older). The juvenile and adolescent forms are commonly combined as late-onset tibia vara. The exact cause of tibia vara remains unknown, although it is thought to involve abnormal growth resultant from excessive weight.

The infantile form of tibia vara is the most common; its characteristics include predominance in black females, approximately 80% bilateral involvement, a prominent medial metaphyseal beak, internal tibial torsion, and leg-length discrepancy (LLD). The characteristics of the juvenile and adolescent forms (late onset) include predominance in black males, normal or greater than normal height, approximately 50% bilateral involvement, slowly progressive genu varum deformity, pain rather than deformity as the primary initial complaint, no palpable proximal medial metaphyseal beak, minimal internal tibial torsion, mild medial collateral ligament laxity, and mild lower extremity length discrepancy. The infantile group has the greatest potential for progression.

An anteroposterior standing radiograph of both lower extremities with patellas facing forward and a lateral radiograph of the involved extremity should be obtained (Fig. 675-10). Weightbearing radiographs are preferred and allow maximal presentation of the clinical deformity. The metaphyseal–diaphyseal angle can be measured and is useful in distinguishing between physiologic genu varum and early tibia vara (Fig. 675-11). Langenskiöld has 6 stages on radiographs (Fig. 675-12). The differentiation is based on fragmentation of the epiphysis, beaking of the medial tibial epiphysis, depression of the medial tibial plateau, and formation of a bony bar. Occasionally, CT with 3-dimensional reconstructions, or MRI, may be necessary to assess the meniscus, the articular surface of the proximal tibia including the posteromedial slope, or the integrity of the proximal tibial physis.

Management is based on the stage of the disease, the age of the child, and nature of presentation (primary or recurrent deformity). In children younger than 3 yr and Langenskiöld stage <3, bracing is effective and can prevent progression in 50% of these children. A maximal trial of 1 yr of orthotic management is recommended. If complete correction is not obtained after 1 yr or if progression occurs during this

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### Table 675-2

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<td><strong>BLOUNT DISEASE</strong></td>
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<td>No significant lateral thrust</td>
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<td>Significant lateral thrust</td>
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Figure 675-8: In recumbent position, tibia and femora are bowed but the legs do not appear bowed. In erect position during weight bearing and with ankles in apposition, the legs are bowed. (From Sluos TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby.)
Figure 675-9 Clinical photograph (A) and standing anteroposterior radiograph (B) of a 5 yr old girl with bilateral early-onset Blount disease. (From Sabharwal S: Blount disease, J Bone Joint Surg Am 91:1758–1776, 2009.)

Figure 675-10 Anteroposterior radiograph of both knees in Blount disease.

Figure 675-11 Metaphyseal-diaphyseal (M-D) angle. Draw a line on the radiograph through the proximal tibial physis. Draw another line along the lateral tibial cortex. Last, draw a line perpendicular to the shaft line as demonstrated in the diagram. (From Morrissey RT, Weinstein SL, editors: Lovell and Winter's pediatric orthopaedics, ed 3, Philadelphia, 1990, Lippincott Williams & Wilkins.)
time, a corrective osteotomy may be indicated. Surgical treatment is also indicated in children >4 yr of age, those at Langenskiöld stage >3, and those with severe deformities. A proximal tibial valgus osteotomy and associated fibular diaphyseal osteotomy are usually the procedures of choice. In late-onset tibia vara, correction is also necessary to restore the mechanical axis of the knee. Hemiplatue elevation with correction of posteromedial slope has also been established as a treatment modality in relapsed cases.

GENU VALGUM (KNOCK-KNEES)
The normal valgus is achieved by 4 yr of age. Variation up to 15 degrees of valgus is possible until 6 yr of age, and thus physiologic valgus has a good chance of correction until this age. The intermalleolar distance with the knees approximated is normally <2 cm, and in a severe valgus deformity it could measure >10 cm. Pathologic conditions leading to valgus are metabolic bone disease (rickets, renal osteodystrophy), skeletal dysplasia, posttraumatic physeal arrest, tumors, and infection. The increased valgus at the knee causes lateral deviation of the mechanical axis with stretching of the medial aspect of the knee leading to knee pain. Deformities >15 degrees and occurring after 6 yr of age are unlikely to correct with growth and require surgical management. In the skeletally immature, medial tibial epiphyseal hemiepiphysiodesis or stapling (guided growth) is attempted for correction. In the skeletally mature, osteotomy is necessary at the center of rotation of angulation and is usually situated in the distal femur. Long-length anteroposterior radiographs of the leg in a weight-bearing stance are necessary for preoperative planning.

Bibliography is available at Expert Consult.

675.5 Congenital Angular Deformities of the Tibia and Fibula
Keith D. Baldwin and Lawrence Wells

POSTEROMEDIAL TIBIAL BOWING
Congenital posteromedial bowing is typically associated with a calcaneovalgus foot and rarely with secondary valgus of the tibia. The exact cause is unknown. Early operative intervention is not indicated because this bowing generally corrects with growth. However, despite the correction of angulation, there is residual shortening in the tibia and fibula. The mean growth inhibition is 12-13% (range: 5-27%). The mean LLD at maturity is 4 cm (range: 3-7 cm). The diagnosis of bowing is confirmed on radiographs, which show the posteromedial angulation without any other osseous abnormalities. The calcaneovalgus deformity of the foot improves with stretching or modified shoe wear and occasionally ankle-foot orthosis. Predicted LLD <4 cm is managed with age-appropriate epiphysiodesis of the normal leg. LLD >4 cm is managed with combination of contralateral epiphysiodesis and ipsilateral lengthening. A corrective osteotomy for distal valgus may be required and can be done in the same setting while correcting LLD.

ANTEROMEDIAL TIBIAL BOWING (POSTAXIAL HEMIMELIA)
Fibular hemimelia is the most common cause of anteromedial bowing of the tibia. The fibular deficiency can occur with complete absence of fibula or a partial development both proximally and distally. It is associated with deformities of femur, knee, tibia, ankle, and foot. The femur is short and has lateral condylar hypoplasia, causing patellar instability and genu valgum deformity. The tibia has anteromedial bowing with reduced growth potential. The keys for management are the ankle stability and foot deformities. The ankle resembles a ball-and-socket joint with lateral instability. The foot deformities are characterized by the absence of lateral digits, equinocavovarus foot, and tarsal coalition.

Various surgical options have been described, and the treatment is tailored to the patient's needs and parents' acceptance. A severely deformed foot could be best managed with Syme or Boyd amputation, with prosthetics as early as 1 yr of age. In the salvageable foot, LLD can be treated with contralateral leg epiphysiodesis or ipsilateral limb lengthening.

ANTEROLATERAL TIBIAL BOWING
Anterolateral tibial bowing is associated with congenital pseudarthrosis of tibia. Fifty percent of the patients have neurofibromatosis, but only 10% of the neurofibromatosis patients have this lesion. The pseudarthrosis or site of nonunion is typically situated at the middle third and distal third of the tibia. Boyd has classified it in increasing severity depending on the presence of cystic and dysplastic changes. The treatment for this condition has been very frustrating, with poor results. Bracing has been recommended to prevent fracture early in the course; however, it has not been successful. Numerous surgical interventions have been attempted to achieve union, such as single- and dual-onlay grafting with rigid internal fixation, intramedullary pinning with or without bone grafting, and an Ilizarov device. With the advent of microsurgery, live fibular grafts have been used with varying results. Because of the poor chances of successful union and considerable LLD, a below-knee amputation with early rehabilitation may be preferred. It is important not to attempt any osteotomy for correction of the tibial bowing.

TIBIAL LONGITUDINAL DEFICIENCY
Tibial longitudinal deficiency follows an autosomal dominant inheritance pattern and has been divided into four types depending on the deficient part of the tibia. The other associated anomalies are foot deformities, hip dysplasia, and symphalangism of the hand. The treatment revolves around presence of proximal tibial anlage and a functional quadriceps mechanism. In type Ia deformity, the proximal tibial anlage is absent and knee disarticulation with prosthesis is recommended. In types Ib and II, the tibial anlage is present and the management consists of an early Syme amputation, followed later by synostosis of the fibula with the tibia, and a below-knee prosthesis. Type III is rare and the principal management is with Syme amputation and a prosthesis. Type IV deformity is associated with ankle diastasis, which requires stabilization of the ankle and correction of LLD at a later stage.

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Bibliography
Bibliography

A discrepancy in the leg lengths may result from a variety of congenital or acquired conditions (Table 676-1). Although up to 25% of the American public may have a difference of more than 1 cm, only a small percentage have more than a 2 cm difference. The main consequence is gait asymmetry. An increase in vertical pelvic motion is observed, and more energy must be expended during ambulation. Although a small compensatory lumbar curvature may develop, there is little evidence to suggest that leg-length discrepancy results in back pain, structural scoliosis, or degenerative arthritis. The goal of treatment is to have a discrepancy of <2-2.5 cm at skeletal maturity, and a variety of treatment methods are available to achieve this objective. Knowledge of the underlying etiology, coupled with regular follow-up to assess limb growth and skeletal maturity, allows the treating physician to project the discrepancy at skeletal maturity and to plan treatment. A subset of patients will have coexisting abnormalities in the viscera or musculoskeletal system, which must be identified and treated as well.

**DIAGNOSIS AND CLINICAL FINDINGS**
Gait asymmetry is the most frequent complaint. The long leg is often kept flexed in stance to level the pelvis. The diagnosis is made on physical examination, and specialized radiographs help to quantify the existing discrepancy and predict what the discrepancy will be at maturity. The discrepancy may be caused by hypoplasia, hyperplasia, or angular deformity (structural discrepancy), by soft-tissue contracture at the hips, knees, or ankles (apparent or functional shortening), or by a combination of these conditions. Other contributing factors include joint subluxation or dislocation (hip), a decrease in the height of the foot (congenital or neuromuscular) or structural disorders of the pelvis. A careful physical examination is required to identify all factors contributing to the discrepancy. Muscle contracture about the hip will also create the appearance of leg-length inequality. For example, to bear weight on an abducted hip, the patient must hike up the contralateral hip and pelvis, making the contralateral leg appear short.

There are several clinical methods for measuring limb length. Our preference is to perform a standing examination, in which blocks of various sizes are placed under the short leg until the pelvis is leveled (Fig. 676-1). An alternate method is to measure the length of each leg with the patient supine by the Galiazzi and Alis tests. The traditional method of using a tape measure is very inaccurate because of, for example, the line of measurement used, muscle atrophy, and moving patients. The range of motion at the hip, knee, and ankle must be also assessed to identify any causes of apparent discrepancy. A 10 degree fixed abduction (or adduction) contracture of the hip will create an apparent leg-length discrepancy of 2-3 cm. Similarly, a flexion contracture of the hip and/or knee will create apparent shortening of the extremity, while an equinus contracture at the ankle will create apparent lengthening of the extremity. A rigid lumbar scoliosis (suprapelvic contracture) will create pelvic obliquity and an associated limb length inequality. Once a discrepancy is quantified, it must be followed at regular intervals until maturity. Assessments at 6-12 mo intervals are most common.

**RADIOGRAPHIC EVALUATION**
The radiologic evaluation complements the clinical examination; both are typically employed when making treatment decisions. Five
different techniques are available. The **teleoroentgenogram** is a single radiographic exposure of both lower extremities (standing) and requires a long cassette. A ruler is placed on the film, and direct measurements are made, factoring in a 6% magnification error. One advantage is that angular deformities may be assessed. Its primary indication is for young children. Unfortunately, as only one exposure is used for the leg and as the ankle is less dense than the hip, it may be difficult to “see” the whole leg. Additionally, because the x-ray source is at the knee projecting up to the hip and down to the ankle, this method projects the hip and ankle along the ruler making the leg appear longer than it really is, particularly in obese patients. The **orthoroentgenogram** consists of 3 separate exposures of the hips, knees, and ankles on a long cassette. The patient is supine, and a ruler is placed on the cassette for measurement of bone length. However, the patient must lie still for the 3 exposures, which is often difficult to achieve in younger children. Because the x-ray beam is pointed at the hip, knee, and ankle in each of the 3 exposures, the length measurement is accurate and each of the 3 joints can be exposed properly. The x-rays expose from the top of the pelvis to the mid femur, from the mid femur to the mid tibia, and from the mid tibia to below the foot for each of the 3 exposures, respectively, permitting angular deformity assessment in the frontal plane only. The **scanogram** also consists of separate exposures of the hips, knees, and ankles on a cassette with a radiographic ruler; a chest sized film cassette is used (Fig. 676-2). There is no magnification error; patients must remain still for the 3 exposures, and angular deformities cannot be assessed. While CT is an accurate technique, the assessment is time-consuming, and the technique is not available in most centers. Additionally a radiologist must normalize the axis of the leg to the screen to accurately measure the limbs. Another technique, called EOS, employs a 3D, low-dose (1/30 to 1/300, the radiation) scanner but requires a sophisticated radiologist to correctly align the limbs for computer measurement. Regardless of the technique it is critical that the patellae be pointed forward, that measurements be made in the plane of the limb, and that the same method be used in sequential measurements to be compared.

In the presence of flexion or extension deformities, each bone should be x-rayed individually with a ruler where the x-ray beam is perpendicular to the bone and the ruler parallel to the bone.

In addition to quantifying the discrepancy, it is essential to determine skeletal age (bone age). An anteroposterior radiograph of the hand and wrist is usually obtained at each visit and compared with the standards in the Greulich and Pyle Atlas to estimate skeletal age. While more accurate techniques are available, most are time-consuming and impractical for routine clinical application. The range of variability using the atlas is approximately 9 mo, so the method is most accurate when multiple data points have been collected.

**TREATMENT**

Options for treatment include observation, a shoe lift or custom orthosis, a limb-shortening procedure (acute shortening and internal fixation vs gradual shortening by growth arrest or guided growth), a limb-lengthening procedure (with internal or external fixation), or a combination of these. Deforrmity correction is often accomplished simultaneously. In the congenital deficiencies (femur, tibia, fibula) in which the predicted limb-length inequality will require more than 3 lengthening operations (more than 20 cm), an early foot amputation may be the best option to achieve an optimal functional outcome. In addition to the magnitude of discrepancy predicted at skeletal maturity, both the anticipated adult height of the patient (estimated from family members) and the desires of the patient and the patient’s family are important considerations.

Discrepancies of up to 2.5 cm may be treated by observation or a shoe lift. Up to 1 cm may be placed within the shoe, and up to 5 cm may be placed on the outside of the shoe. Complete correction of inequality is not required, and the height of the lift should be adjusted based on the patient’s gait and comfort. An orthotic may be used as a temporizing measure prior to definitive treatment. For extended discrepancies, “foot in foot” prostheses are a reasonable alternative until limb length can be accomplished or for patients who cannot or do not wish to undergo surgical correction.

For patients with a discrepancy between 2 and 5 cm, an **epiphysiodesis** is offered in skeletally immature patients, and an acute shortening may be performed in a skeletally mature patient. Epiphysiodesis refers to a temporary or permanent cessation of growth at 1 or more physes. A permanent growth arrest is most commonly performed as long as sufficient data are available with which to accurately predict when to perform the procedure. Approximately 65% of the growth of the lower extremity comes from the distal femur (37%, 9 mm/yr) and proximal tibia (28%, 6 mm/yr). Males typically grow until 16 yr of age, whereas females grow until 14 yr of age. As such, performing an epiphysiodesis of both the distal femur and the proximal tibia in a patient with 3 yr of growth remaining should achieve approximately 4.5 cm of correction. Techniques used to determine the timing of epiphysiodesis are the Menelaus method (“rule of thumb”), the Green and Anderson method, the Moseley straight-line graph, and the multiplier method (Figs. 676-3, 676-4, and 676-5). The most common surgical technique is the percutaneous epiphysiodesis, in which the physis is ablated with a drill and curette under image intensification. This is an outpatient procedure with few complications. Insertion of plates and screws or just screws across the physis is an alternative but usually requires a second operation to remove the hardware. For patients for whom sufficient data are unavailable or those for whom the underlying diagnosis is associated with an unpredictable pattern of growth, then a reversible technique, such as staples, plates, and/or screws, may be considered. Once equalization has been achieved, the hardware can be removed, allowing growth to resume. When the patient is skeletally mature or if it is deemed appropriate to wait until maturity before treatment, acute shortening may be the best option. Acute shortening is typically performed at the femur (several techniques have been described), given the increased risk of complications (compartment syndrome, neurovascular problems) associated with shortening of the tibia and fibula.
Growth Remaining in Normal Distal Femur and Proximal Tibia Following Consecutive Skeletal Age Levels

Means and standard deviations derived from longitudinal series 50 girls and 50 boys.

**Figure 676-3** Growth remaining charts for girls and boys. The growth remaining charts for girls and boys are different. Actual correction is based on growth of the short limb. To use the chart correctly, the discrepancy at maturity and the percentage of growth retardation of the short limb should be calculated. (Redrawn from Anderson M, Green WT, Messner MB: Growth and predictions of growth in lower extremities. J Bone Joint Surg Am 45:1–4, 1963.)

**Figure 676-4** The Moseley straight-line graph for the assessment of leg-length inequalities. This allows simultaneous correlation of the normal leg, short leg, and bone age of the child. It will accurately predict lengths of each extremity at skeletal maturity. The reference slopes are used as a guide in determining when appropriate treatment should be performed. (From Moseley CF: A straight-line graph for leg-length discrepancies. J Bone Joint Surg Am 59:174–179, 1977.)
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Multiplier for Boys and Girls
(Paley et al, 1999)

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LLD Prediction Formulas

Prenatal LLD (congenital)
\[ \Delta_m = \Delta \times M \]

Postnatal LLD (developmental)
\[ \Delta_m = \Delta + I \times G \]

Inhibition = \( I = 1 - \frac{S - S^*}{L - L^*} \)

Growth remaining = \( G = L(M - 1) \)

\[ \Delta_m = \text{LLD at maturity} \]

\[ \Delta = \text{Current LLD} \]

\[ \text{L} \& \text{S} = \text{Current length of long and short leg} \]

\[ \text{L}^* \& \text{S}^* = \text{Length of long and short leg at any other date since LLD began} \]

For discrepancies >5 cm, lengthening of the short limb is the procedure of choice. An exception would be a discrepancy secondary to overgrowth of 1 limb, in which limb shortening would be preferred so as to preserve body proportions, for which acute or gradual shortening of the abnormal limb is preferred. Patients with anticipated discrepancies greater than 8-10 cm often require 1 or more limb-lengthening procedures (several years apart) with or without an epiphysiodesis. The most common technique used for limb lengthening involves placement of an external fixator, either a ring fixator such as the Ilizarov device or a monolateral device (Fig. 676-6). The bone is cut at the metaphyseal-diaphyseal junction, and lengthening is achieved gradually through distraction at the corticotomy. The usual rate of lengthening is 1 mm/day, and it takes approximately 1 mo wearing the fixator for each centimeter of length gained with a minimum of 3 mo in the fixator. Additional time in the fixation may be required for pathologic bone or for metabolic diseases affecting bone formation. A maximum of 15-25% of the original length of the bone may be gained at each session. An advantage of the circular fixator or multiaxial external fixators is the ability to correct coexisting angular deformities at the same time. Technologic advances have allowed the development of intramedullary lengthening and compression rods driven by external magnets. These may provide improvements in patient satisfaction and reduced complications.

Complications include pin tract infection (most common), wound infection, hypertension, joint subluxation, muscle contracture, premature consolidation, delayed union, implant-related problems, and fractures after implant removal. Finally, early amputation and prosthetic fitting may provide the best long-term function in patients with projected discrepancies in excess of 18-20 cm, especially when there are coexisting deformities or deficiencies of the ipsilateral foot (Figs. 676-7 and 676-8). The alternative would be multiple reconstructive procedures throughout childhood and adolescence. The impact of multiple procedures on the child's psychosocial development must also be kept in mind when formulating the treatment plan in these complex cases.

Bibliography is available at Expert Consult.
Bibliography
Figure 676-8 Anteroposterior radiograph of fibular hemimelia with leg-length discrepancy.
Discoid lateral meniscus (DLM) is a congenital anatomic variation of the lateral meniscus that may be asymptomatic or cause the classic snapping knee syndrome. Because of asymptomatic cases, the true incidence is difficult to determine, but it is estimated to occur in 3-5% of children and adolescents. Up to 25% of DLM cases may be bilateral. Previously thought to result from a failure of an embryologic sequence of degeneration at the center of the meniscus, discoid menisci have been subsequently shown to not be the developmental precursors for normal menisci.

Anatomically, the normal meniscus (Fig. 677-1A) is attached around its periphery and at the tips of the C anteriorly and posteriorly onto the tibia. During knee motion, the meniscus translates anteriorly and posteriorly to match the slight rollback of the lateral femoral condyle on the tibia with knee flexion. However, with a DLM, the meniscal tissue trapped between the articular surfaces is pushed anteriorly as the knee flexes. These abnormal forces, over time, result in tears in the meniscal tissue or in the posterior attachments, creating excessive meniscal displacement anteriorly during knee flexion. This produces a pop when flexing, usually at about 90-120 degrees of knee flexion as the meniscus is extruded anteriorly, and a loud click or clunk when extending the knee, usually in the last 30 degrees of extension, as the meniscus reduces back between the joint surfaces.

There are 3 types of DLM, according to the widely used Watanabe classification. Type I, or complete, most commonly produces symptoms and is characterized by a thickened lateral meniscus with complete coverage of the tibial surface (see Fig. 677-1B). Meniscus tissue is always between the joint surfaces. Type II, or incomplete, is of variable size and covers a lower percentage of the tibial surface (see Fig. 677-1C) compared to the complete type. Although they can become stretched or torn over time, both the complete and the incomplete types are thought to develop with normal peripheral attachments. Type III, or the Wrisberg ligament type DLM is extremely mobile. Although its shape is not necessarily discoid, the hypermobility of the posterior portion of the meniscus allows it to be extruded anteriorly with flexion and for it to pop back in place with extension, as is characteristic of the other DLM variants.

CLINICAL MANIFESTATIONS AND DIAGNOSIS
The complete and incomplete types of DLM can be asymptomatic, especially if they have stable peripheral attachments. A symptomatic DLM in early childhood is usually caused by a meniscal tear or absent peripheral attachments allowing for the anterior extrusion during flexion and reduction with extension, producing the classical snapping knee. These patients can present as early as 2 yr of age, but more commonly present after approximately 6 yr of age; most patients present with symptoms during their teenage years. As these patients gain weight with their adolescent growth spurt, they place increasing static and dynamic loads on the tissue, often with high-level sports. Degeneration in the central portion of the DLM with direct weight bearing makes the meniscus highly susceptible to injury and tears, producing lateral pain and swelling in the knee. Often, the classic popping is not appreciated in these patients.

Younger children usually present with no history of trauma or acute inciting event and with a complaint of popping in the knee with patellofemoral pain and swelling. Patellar tendinitis and lateral patellar ligamentous syndromes are often considered in the differential diagnosis of lateral knee pain. The clinical diagnosis of DLM in these patients can be made by palpating the prominent meniscofemoral ligament, or ligament of Wrisberg, that secures the posterior horn of the lateral meniscus to the lateral surface of the medial femoral condyle (see Fig. 677-1D). As a result, the Wrisberg ligament type DLM is extremely mobile. Although its shape is not necessarily discoid, the hypermobility of the posterior portion of the meniscus allows it to be extruded anteriorly with flexion and for it to pop back in place with extension, as is characteristic of the other DLM variants.

Chapter 677
The Knee
Eric J. Sarkissian and J. Todd R. Lawrence

NORMAL DEVELOPMENT OF THE KNEE
The knee, a major synovial joint, forms between the 3rd and 4th mo of fetal development, with secondary ossification centers forming between the 6th and 9th fetal mo at the distal femur and between the 8th fetal mo and the 1st postnatal mo at the proximal tibia. The patellar ossification center appears between the ages of 2 and 4 yr in girls and 3 and 5 yr in boys.

ANATOMY AND RANGE OF MOTION
The knee is the largest joint in the body and acts primarily as a modified hinge. The distal femur is cam shaped with the medial and lateral femoral condyles having slightly different shapes. This allows for a posterior gliding motion of the femur on the tibial plateau to occur during knee flexion. This also permits about 8-12 degrees of rotation through the flexion and extension arc. The normal range of motion of the knee is from neutral (or fully straight) to 140 degrees of flexion. Increased ligament laxity including hyperextension of up to 10-15 degrees can be normal in many children. Most activities can be performed in the flexion arc of 0-70 degrees.

The knee consists of three articulations: patellofemoral, tibiofemoral, and tibiofibular. The anterior and posterior cruciate ligaments as well as medial and lateral collateral ligaments stabilize the knee during movement. The medial and lateral menisci provide support under compressive forces, helping to redistribute the forces from the more rounded distal femur to the more flat proximal tibia. The medial patellofemoral ligament is the primary static soft-tissue restraint against lateral patellar displacement. There are also several bursae located about the knee to cushion and reduce friction on tendons acting across the knee joint.
occasional swelling. Older children and adolescents often can recall an inciting event and will sometimes report the mechanical popping, but more often note the lateral joint line pain and knee swelling. Physical examination might show a mild effusion and tenderness over the lateral joint line. With knee flexion, a pop with a slight protuberance along the lateral joint line anteriorly can sometimes be appreciated as the meniscus is extruded anteriorly. As the knee is brought back into extension at approximately 20-30 degrees short of full extension, the meniscus can be felt to snap back into the joint and the protuberance at the lateral joint line disappears.

A high index of suspicion is necessary based on history and clinical exam findings. Standard anteroposterior, lateral, merchant (patellar), and 45 degrees flexed posteroanterior (tunnel) views should be obtained if this diagnosis is considered. Radiography of the knee may show widening of the lateral aspect of the knee joint, flattening of the lateral femoral condyle resulting in a squared-off appearance, and cupping of the lateral aspect of the tibial plateau. Because these findings are very nonspecific, with any history or physical examination findings suggestive of a DLM, evaluation with MRI provides a definitive diagnosis.

**TREATMENT**

Patients with asymptomatic or incidentally found DLM without evidence of a tear or meniscal instability are treated nonoperatively with observation. They should be educated on symptoms to watch out for, but no activity restrictions are often necessary. If knee pain or mechanical symptoms limit activity or a meniscal tear develops, consideration is given for surgical intervention. Partial meniscectomy, referred to as saucerization, is often performed to reshape the meniscus arthroscopically with the goal of obtaining an anatomically normal-appearing meniscus (Fig. 677-2). Tears remaining in what would be the normal rim of meniscal tissue are either repaired or excised. Meniscal instability is also addressed with repairs as appropriate. If tears extend all the way to the periphery of the meniscus, sometimes a total meniscectomy, or complete excision of the meniscus, may be necessary. Because this leaves the joint surfaces unprotected and can lead to early osteoarthritis, addressing DLM tears as soon as they develop and before they extend to the periphery is preferred.
Bibliography
Popliteal cysts, or Baker cysts, are cystic masses filled with gelatinous material that develop in the popliteal fossa, the shallow depression located at the posterior part of the knee. They are considered rare in children. They most commonly occur in the region of the medial head of the gastrocnemius and semimembranosus. They occur as an isolated fluid-filled bursa or via herniation through the posterior joint capsule of the knee into this same location. Histologically, the cysts are classified as fibrous, synovial, inflammatory, or transitional. Typically, popliteal cysts resolve spontaneously, although the process may take several years.

Clinical Manifestations and Diagnosis

Patients commonly present with a mass behind the knee that may be fairly large when first noted. There are usually no symptoms of internal derangement of the knee. Physical examination reveals a firm mass in the popliteal fossa, often medially located and distal to the popliteal crease. The mass is usually most prominent when the knee is extended. Transillumination of the cyst on physical examination is a simple diagnostic test. Knee radiographs are normal and should be obtained to identify other lesions, such as osteochondromas, osteochondritis dissecans, and malignancies. The diagnosis may be confirmed by ultrasonography, MRI, or aspiration. Ultrasound differentiates a solid mass from a cystic lesion. In the presence of a knee effusion, consideration should be given to an MRI to evaluate for knee intraarticular pathology that may be causing the swelling, such as a meniscal tear or a DLM. These children should also be assessed for other pathology that may cause recurrent or intermittent knee effusions, including Lyme disease, juvenile idiopathic arthritis, or other autoimmune processes. The presence of a solid mass detected on ultrasound or MRI warrants additional diagnostic testing and referral for biopsy consideration.

Treatment

In most cases, popliteal cysts are observed because they often resolve spontaneously. Rest and leg elevation are beneficial to promote drainage of fluid accumulating within the cyst. If necessary, aspiration can reduce the size of the cyst and a corticosteroid injection can reduce inflammation. Cysts will often recur after aspiration. Surgical excision of a popliteal cyst is indicated only when symptoms are debilitating and have not resolved after several months.

Bibliography is available at Expert Consult.

677.3 Osteochondritis Dissecans

Eric J. Sarkissian and J. Todd R. Lawrence

Osteochondritis dissecans (OCD) is a localized pathologic process of the subchondral bone that secondarily affects the overlying articular cartilage and can progress to cartilage separation and fragmentation. The precise cause for OCD remains unclear, although repetitive microtrauma appears to be the leading candidate. Roles for genetics and ischemia have also been implicated in the etiology. The disorder is being seen with rising frequency in children and adolescents, likely in large part, as a consequence of increased sports participation in young athletes. In the knee, OCD most commonly affects the lateral aspect of the medial femoral condyle. The lateral femoral condyle and patella may also be affected, as well as joints other than the knee, such as the elbow or ankle. Characteristic pathology of the lesion includes an area of avascular necrosis in the subchondral bone, the segment of bone just below the joint surface, and varying degrees of ischemia and fibrosis of the overlying hyaline cartilage. Failure of both the bone and the cartilage surface to heal completely is associated with an increased risk for developing premature osteoarthritis.

Clinical Manifestations and Diagnosis

The most common presenting complaint is a vague or deep knee pain that may localize along the medial or lateral joint line. If the osteochondral fragment becomes unstable, the patient may also develop mechanical symptoms, such as catching or locking. Physical examination findings include effusion, tenderness to palpation over the femoral condyles, quadriceps atrophy, and diminished range of motion.

Because most OCD lesions are located more on the posterior aspect of the femoral condyle, a posteranterior radiograph with a 45-degree flexed knee (tunnel view) is often required to evaluate for the presence of an OCD. Many of these patients also have some degree of patellar-related pain, necessitating merchant (patellar) view plain films. Thus, standard radiographic evaluation of nontraumatic adolescent knee pain should routinely include anteroposterior, lateral, tunnel, and merchant radiographs of the knee. An early lesion may appear as a small radiolucency at the articular surface. A more advanced lesion may have a well-demarcated segment of subchondral bone with a lucent line demonstrating separation from the condyle. In children younger than age 10 yr, irregularities in the ossification center of the developing epiphysis may be difficult to distinguish from an OCD lesion.

MRI is useful for determining the size of the OCD, integrity of the articular cartilage, and presence of loose bodies. Fluid observed between the fragment and subchondral bone suggests an unstable lesion and high risk for detachment. Any linear signal through the articular cartilage or displacement of the fragment indicates a potentially unstable lesion as well. For an unstable-appearing OCD, either based on the patients’ symptoms and signs, or the imaging, arthroscopy should be performed to evaluate the status of the lesion.

Treatment

Treatment for juvenile OCD includes nonoperative and surgical management, with treatment decisions being based on many factors, including the growth status and skeletal maturity of the patient, the presence of symptoms, the lesion size, and whether the lesion appears intact and stable or if there is any suggestion of instability. Skeletal immaturity (i.e., younger age), smaller lesion size, and the absence of mechanical symptoms or pain have been associated with a higher likelihood of OCD healing with nonoperative treatment. Unstable lesions will not usually heal with conservative treatment.

Thus, young patients with stable lesions, as evidenced by an intact articular surface on imaging (Fig. 677-3A), are deemed to have an acceptable probability of healing and are often initially managed conservatively with a period of non–weightbearing and immobilization, followed by a period of strict activity restriction and physical therapy for 3-6 mo. OCD healing is followed with radiographs, usually at approximately 3 mo intervals, until lesion healing has been noted. If healing has not been radiographically confirmed in 3-6 mo, surgical intervention is often considered. Because of the low rate of healing in skeletally mature patients, even intact lesions are not usually managed conservatively in this patient population, but recommended for surgery.

Although nonsurgical treatment can be successful in intact lesions, surgical treatment of intact lesions is often more successful and induces healing at a faster rate. Consequently, patients often choose to pursue early surgical intervention. For stable and intact lesions, surgical management involves arthroscopic evaluation of the joint followed by either a transarticular or retroarticular drilling to stimulate bony healing by creating channels in the subchondral bone that allow revascularization to occur. Both techniques are comparably effective in producing short-term patient-oriented outcomes and radiographic healing.

More advanced lesions with edema beneath the fragment, subchondral cyst formation, and partial (see Fig. 677-3B) or complete (see Fig. 677-3C) fragment detachment on arthroscopy are potentially salvageable. Treatment involves drilling or fixation with possible bone grafting. OCD lesions may progress to become unstable and dislocate into the joint space (see Fig. 677-3D). Removal of the loose body in addition to cartilage repair and restoration are typically performed for such unsalvageable lesions. In the postoperative period, patients undergo
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The Knee tendon (OS disease). Diagnosis is usually made clinically, but radiographs may reveal fragmentation of the tibial tubercle and soft tissue swelling (Fig. 677-5).

TREATMENT

In most patients, Sinding-Larsen-Johansson syndrome and OS disease are self-limited processes and resolve with rest. Patients are treated with an escalating treatment regime until they are pain free with activity. If they are pain free with normal daily activities, they may maintain this level of activity for 2 additional wk. In more-severe cases, a knee immobilizer or even crutches with restricted weightbearing are required to get the patient comfortable. Patients are usually advised to maintain a level of activity for 1-2 wk before attempting to advance. Sports and other dynamic activities are restricted until the patient has been pain free to palpation for at least 2 wk. During this rest period, addressing some of the contributing factors, such as muscular tightness, can help prevent recurrence with activity resumption. A self-directed stretching regime concentrating on the quadriceps and hamstrings may be provided. Some patients and resistant cases may benefit from formal instruction in these exercises with a physical therapist.

In skeletally immature patients, the tibial tubercle is an extension of the proximal tibial epiphysis. As the femur rapidly grows in length, patients often develop tight musculature, particularly of the quadriceps, across the knee joint. These patients also develop movement patterns that preferentially place stress at the knees during activities instead of distributing that stress across other joints in the lower extremity. The repetitive tensile microtrauma sustained during sports or other athletic activities then creates traction injuries at the weak points in the extensor mechanism at the knee, as the stress exceeds the developing skeleton's ability to repair the damage.

Sinding-Larsen-Johansson syndrome is an insertional periostitis at the inferior pole of the patella. Osgood-Schlatter (OS) disease is an irritation of the patellar tendon at its insertion into the tibial tubercle or a traction apophysitis of the tibial tubercle growth plate. These conditions typically present during periods of relative accelerated growth. Sinding-Larsen-Johansson syndrome tends to occur in a slightly younger patient population, whereas OS disease presents in slightly older patients with most symptomatic between the ages of 10 and 15 yr. These conditions are most common in very physically active boys. However, as the number and intensity of female athletics has increased, the incidence in females seems to be on the rise.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Anterior knee pain, very specifically localized to the inferior pole of the patella (Sinding-Larsen-Johansson syndrome) or over the tibial tubercle (OS disease) is the most common patient complaint. Swelling, as well as an eventual firm and fixed increased prominence at the tibial tubercle, may occur with OS disease and may also be part of the initial complaint (Fig. 677-4). There is typically no acute traumatic inciting event. The pain is aggravated by sports activities, but may often persist with daily activities and even at rest. Physical examination reveals point tenderness over the tibial tubercle and the distal portion of the patellar
tendon (OS disease). Diagnosis is usually made clinically, but radiographs may reveal fragmentation of the tibial tubercle and soft tissue swelling (Fig. 677-5).

TREATMENT

In most patients, Sinding-Larsen-Johansson syndrome and OS disease are self-limited processes and resolve with rest. Patients are treated with an escalating treatment regime until they are pain free with activity. If they are pain free with normal daily activities, they may maintain this level of activity for 2 additional wk. In more-severe cases, a knee immobilizer or even crutches with restricted weightbearing are required to get the patient comfortable. Patients are usually advised to maintain a level of activity for 1-2 wk before attempting to advance. Sports and other dynamic activities are restricted until the patient has been pain free to palpation for at least 2 wk. During this rest period, addressing some of the contributing factors, such as muscular tightness, can help prevent recurrence with activity resumption. A self-directed stretching regime concentrating on the quadriceps and hamstrings may be provided. Some patients and resistant cases may benefit from formal instruction in these exercises with a physical therapist.

Bibliography is available at Expert Consult.
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Reassurance is important, because some patients and parents fear that the swollen tubercle may be a sign of malignancy. Patients and family members should be advised, however, that the tubial tubercle swelling will not likely resolve. Hyperosmolar dextrose local injections may improve outcomes in patients with recalcitrant disease. Removal of ossicles from the tubercle is rarely necessary in pediatric patients but may be required with persistent disabling symptoms in young adults. Complications are rare and include early closure of the tubial tubercle with recurvatum, or hyperextension, deformity, and rarely, patellar tendon rupture or avulsion fracture of the tubial tubercle. Although rare, these complications can have significant long-term consequences and should thus prompt counseling to avoid playing through the pain.

Bibliography is available at Expert Consult.

_677.5 Patellofemoral Pain Syndrome_

Eric J. Sarkissian and J. Todd R. Lawrence

Also known as anterior knee pain syndrome, patellofemoral pain syndrome (PFPS) is one of the most common causes of knee pain, particularly in adolescent girls. Previously, PPSS was thought to arise from a deranged patellar articular surface, hence, the former term chondromalacia patella. Increasing evidence shows that anterior knee pain is frequently present even with normal articular cartilage of the patella, resulting in more appropriate labeling of the condition. The precise etiology of the knee pain remains unknown and is likely multifactorial.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

Pain beneath or near the patella is the most common symptom. Classically, walking up and down stairs, which puts the patella under high compressive loads, aggravates the pain. Squatting, running, and other vigorous physical activities also exacerbate the anterior knee pain. Sitting in a flexed knee position for an extended period of time, the so-called theater sign, is another common complaint. There is usually no history of antecedent trauma, although falling onto a flexed knee is sometimes noted. Buckling or a sense of the knee giving way can occur, but there is rarely any true knee instability. Swelling is not common and if present should prompt further investigation. Pain is often relieved through knee extension.

Physical exam reveals isolated tenderness with palpation about the medial or lateral aspects of the patella. With the knee extended and the quadriceps relaxed, placing pressure on the patella and translating it distally into the top of the trochlear groove, the so-called grind test, often also causes pain. Reproduction of the patient’s pain with these maneuvers is an important component of the exam. Active and passive range of motion of the knee, alignment of the lower extremity, knee ligamentous stability, patellar tracking, and gait should be evaluated to identify any obvious causes of malalignment or an unstable patella. These patients often have tight quadriceps, hamstring, and heel cords, as well as weak hip musculature and poor overall balance. A single leg squat can often highlight the hip weakness and balance and alignment issues that contribute to this condition. Routine radiographs of the knee, including anteroposterior, lateral, tunnel (posterolateral with 45 degrees flexed knee), and Merchant (patellar) views, are usually normal, but are helpful in eliminating other etiologies. Radiographs of the hip should be considered in suspected cases to rule out hip pathology, such as a slipped capital femoral epiphysis, that can manifest as ill-defined knee pain in adolescents as well. An MRI is not routinely required for evaluation but should be considered in any patient with a history of mechanical symptoms or an effusion.

**TREATMENT**

Several methods of nonoperative treatment are utilized to address PFPS. The mainstay of treatment is continued physiotherapy, involving overall lower-extremity stretching and strengthening, including short-arc quadriceps strengthening, hip and core strengthening, and exercises designed to address balance and overall body positioning during dynamic activities. No one particular regime seems to demonstrate results superior to the others. Home exercise programs can be effective for the properly disciplined and motivated patient, but formal physical therapy should be considered in resistant cases or in patients who may not have the motivation or wherewithal to adhere to a self-directed program. Orthoses, including patellar taping, knee sleeves, customized knee braces, or even shoe inserts are often used in conjunction with physical therapy. However, evidence for long-term benefit from orthotic use is unclear. Treatment with Botulinum toxin injections, nonsteroidal antiinflammatory medications, or therapeutic ultrasound is not substantiated. Most cases of PFPS resolve spontaneously over a period of years. Arthroscopic evaluation of the knee and patellofemoral joint is rarely necessary.

Bibliography is available at Expert Consult.

_677.6 Patellofemoral Instability_

Eric J. Sarkissian and J. Todd R. Lawrence

Patellofemoral joint stability depends on a balance of the static restraints and the dynamic forces acting on the patella. These include the restraining ligaments and the articular anatomy of the patellofemoral groove that serve to balance the dynamic forces of the quadriceps mechanism and overall limb positioning. During knee flexion, the pull of the quadriceps mechanism tends to place an overall lateral displacing force at the patella. The Q angle refers to the deviation between the angle of the patellar tendon and the line of the quadriceps. Wider hips and valgus (knock-kneed) positioning increase the Q angle and thus the lateral force applied at the patella. In extension, the static restraints, including the medial restraining ligaments, primarily the medial patellofemoral ligament, are responsible for guiding the patella into the trochlear groove in the distal femur. The pull of the vastus medialis obliquus is the only dynamic restraint. Once in the trochlea, the bony congruity becomes the primary restraint to the net lateral muscular forces.

Factors that contribute to patellofemoral instability are multifactorial and include vastus medialis insufficiency, ligamentous laxity, shallow sulcus, condylar hypoplasia, patella alta (high riding patella), or malalignment that effectively increases the Q angle, such as genu valgum, internal femoral torsion, or external tibial torsion.

**Acute patellofemoral dislocation** is the most common acute knee disorder in children and adolescents and often occurs after a sudden valgus strain during a sporting activity but may be the result of direct
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trauma. Recurrent patellofemoral subluxation is more than 1 episode of patellar subluxation without frank dislocation. Lateral malalignment of the quadriceps mechanism is the most common etiologic factor. Habitual dislocation of the patella describes patellar dislocation occurring during every knee flexion. A dysplastic knee with contracture of the lateral portion of the quadriceps mechanism is often associated. Several syndromes are associated with patellar instability, including Down syndrome (see Chapter 81), Turner syndrome (see Chapter 81), Kabuki syndrome, and Rubinstein-Taybi syndrome.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

With an acute patellar dislocation, patients will recall the acute event and the sensation that their knee cap was out of place. Straightening the knee is all that is usually required to reduce the patella, but sometimes this requires medical attention. Swelling is usually almost immediate following the injury and appreciable on examination with an effusion. The patella may appear laterally displaced when the knee is fully extended or higher than normal with the knee slightly flexed. Pain along the medial knee from the medial patella to the medial epicondy of the femur is common. Lateral patellar translocation with the knee slightly flexed should be tested with the **patellar apprehension test**.

In the acute setting there will be increased translation and pain as well as a feeling of insecurity. Patellar tracking is also an important component to the exam but may not be possible due to pain in the acute setting. The **J sign** refers to the inverted J-path the patella takes, beginning in a laterally subluxated position and then suddenly shifting medially to engage the femoral groove with early knee flexion. The torsional profile of the patient is also important to assess to rule out possible rotational abnormalities of the femur or tibia.

Radiographs of a patient with patellar instability should include anteroposterior, lateral, and merchant views (obtained with the knee bent 45 degrees, with the beam of the x-ray through the knee from head to toe) of the patella. Radiographs should also be carefully examined for occult fractures. In the presence of a significant knee effusion, mechanical symptoms, acute traumatic patellar dislocation, or uncertainty in the diagnosis, further investigation may warrant an MRI to evaluate for loose bodies or cartilage damage. MRI will illustrate bone bruise patterns typical of patellar dislocation at the medial patellar facet and at the lateral femoral condyle. A tear in the medial patellofemoral ligament may also be seen, especially in cases of an acute patellofemoral dislocation.

**TREATMENT**

Nonoperative management is initially recommended for acute patellar dislocation and recurrent patellar subluxation, unless an osteochondral fracture or additional intra-articular pathology is seen on imaging studies. Although early physical therapy has also been shown to be successful, a brief 4-6 wk period of immobilization in full extension may help with healing of the medial knee restraints following an initial traumatic dislocation. After this, transition to a patellar stabilizing brace usually improves symptoms. Successful treatment is usually achieved with formal physical therapy aimed at improving extensor muscle tone, particularly the vastus medialis obliquus, activity-related body positioning, and hip and core muscle strengthening. The reported redislocation rate following an initial traumatic patellar dislocation ranges from 15-44%.

Failure to improve after nonoperative treatment and persistent episodes of patellar subluxation or dislocation are indications for surgical intervention to address patellofemoral instability. Patients with loose bodies, osteochondral fractures, or chondral damage are surgical candidates for early intervention. Many different types of surgical procedures exist to prevent lateral excursion of the patella from occurring. These include proximal realignment of the patella, distal realignment of the patellar tendon insertion, lateral release, medial patellofemoral ligament reconstruction, or guided growth techniques. The surgical approach that is selected should be individualized for each patient depending on the pathoanatomy contributing to the recurrent subluxations or dislocations.

Pediatric anterior cruciate ligament (ACL) reconstruction has become more prevalent as ACL tears in skeletally immature patients have greatly increased in recent years. Increased sports participation, increased intensity of training and competition, participation on multiple teams, heightened awareness, and improved methods for diagnosis are all cited as contributing factors to the growing awareness of ACL injuries in children and adolescents.

Females are also known to have a greater risk for ACL injury than males. The gender-specific discrepancy appears to be caused mostly by insufficient neuromuscular activation patterns in females, resulting in increased genu valgum, or knock-knee, biased landing and, therefore, a heightened tendency toward landing or stopping in an injury prone position. Various pediatric ACL injury prevention programs show benefit in not only reducing the rate of injuries but also in increasing athletic strength and performance.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

The majority of ACL tears occurs as a result of a noncontact injury. Patients may report a pop associated with the acute onset of knee pain. Later they develop swelling, limited range of motion, and sometimes a sensation of instability. After the initial injury, patients may have surprisingly little pain. On physical exam, the anterior drawer sign or Lachman test may indicate increased anterior tibial translation. The Lachman examination is performed by applying an anteriorly directed force to the proximal tibia with the femur stabilized and the knee flexed 20-30 degrees. The amount of translation and the end point are assessed, with increased translation and an indistinct end point indicating a positive test. A pivot shift test can also be performed to confirm the diagnosis but is rarely successful in the conscious patient. It is conducted by gently bending the knee while just supporting the lower leg. A gentle valgus stress and slight internal rotation can enhance the shift.

Radiographs of the knee are performed, including anteroposterior, lateral, tunnel (posteroanterior with 45 degrees flexed knee), and merchant (patellar) views, to assess for other potential injuries common in pediatric and adolescent patients, such as tibial spine avulsion fractures or OCD. In traumatic injuries, internal and external oblique radiographs can also be helpful. Ultimately, knee MRI can confirm the presence of an intrasubstance ACL tear, as well as meniscal or chondral pathology. Arthroscopic evaluation is the gold standard for diagnosis and treatment.

**TREATMENT**

The management of ACL injury in this patient population can be challenging and the severity of the ACL tear is important to differentiate. Incomplete ACL tears may be treated nonoperatively and the patient and family’s understanding and willingness to adhere to a protocol of bracing and activity restriction are important factors in optimizing outcomes. For complete tears of the ACL, because of the risk of ongoing knee damage if stabilization of the knee is delayed, surgical reconstruction is now recommended for patients who are physically, mentally, and emotionally capable after a thorough discussion with the patient and family about the risks and benefits. All-epiphyseal, partial transphyseal, or traditional transphyseal reconstruction techniques are used based upon the skeletal maturity of the patient to minimize the risk for growth disturbance across the distal femoral and proximal tibial physis.

Depending on the technique used for reconstruction and any associated meniscal pathology addressed, weight bearing is restricted and a brace is used for the 1st 4-6 wk postoperatively. Physical therapy is used postoperatively and continued until strength and functional testing are equal to the contralateral, unaffected limb. Routine follow-up visits and radiographs are conducted to monitor progress and signs of growth disturbance. Patients return to sports typically at a minimum of 9 mo postoperatively and are followed on a yearly basis thereafter until skeletal maturity.

Bibliography is available at Expert Consult.
Bibliography


Bibliography
Anatomically, the hip joint is a ball-and-socket articulation between the femoral head and acetabulum. The hip joint is a pivotal joint of the lower extremity, and its functional demands require both stability and flexibility.

**GROWTH AND DEVELOPMENT**

The hip joint begins to develop at about the 7th wk of gestation, when a cleft appears in the mesenchyme of the primitive limb bud. These precartilaginous cells differentiate into a fully formed cartilaginous femoral head and acetabulum by the 11th wk of gestation (see Chapter 8). At birth, the neonatal acetabulum is completely composed of cartilage, with a thin rim of fibrocartilage called the labrum.

The very cellular hyaline cartilage of the acetabulum is continuous with the triradiate cartilages, which divide and interconnect the 3 osseous components of the pelvis (the ilium, ischium, and pubis). The concave shape of the hip joint is determined by the presence of a spherical femoral head.

Several factors determine acetabular depth, including interstitial growth within the acetabular cartilage, appositional growth under the perichondrium, and growth of adjacent bones (the ilium, ischium, and pubis). In the neonate, the entire proximal femur is a cartilaginous structure, which includes the femoral head and the greater and lesser trochanters. The 3 main growth areas are the physeal plate, the growth plate of the greater trochanter, and the femoral neck isthmus. Between the 4th and 7th mo of life, the proximal femoral ossification center (in the center of the femoral head) appears. This ossification center continues to enlarge, along with its cartilaginous anlage, until adult life, when only a thin layer of articular cartilage remains. During this period of growth, the thickness of the cartilage surrounding this bony nucleus gradually decreases, as does the thickness of the acetabular cartilage. The growth of the proximal femur is affected by muscle pull, the forces transmitted across the hip joint with weight bearing, normal joint nutrition, circulation, and muscle tone. Alterations in these factors can cause profound changes in the development of the proximal femur.

**VASCULAR SUPPLY**

The blood supply to the capital femoral epiphysis is complex and changes with growth of the proximal femur. The proximal femur receives its arterial supply from intraosseous (primarily the medial femoral circumflex artery) and extraosseous vessels (Fig. 678-1). The retinacular vessels (extraosseous) lie on the surface of the femoral neck but are intracapsular because they enter the epiphysis from the periphery. This makes the blood supply vulnerable to damage from septic arthritis, trauma, thrombosis, and other vascular insults. Interruption of this tenuous blood supply can lead to avascular necrosis of the femoral head and permanent deformity of the hip.

**678.1 Developmental Dysplasia of the Hip**

Developmental dysplasia of the hip (DDH) refers to a spectrum of pathology in the development of the immature hip joint. Formerly called congenital dislocation of the hip, DDH more accurately describes the variable presentation of the disorder, encompassing mild dysplasias as well as frank dislocations.

**CLASSIFICATION**

Acetabular dysplasia refers to abnormal morphology and development of the acetabulum. Hip subluxation is defined as partial contact between the femoral head and acetabulum. Hip dislocation refers to a hip with no contact between the articulating surfaces of the hip. DDH is classified into 2 major groups: typical and teratologic. Typical DDH occurs in otherwise normal patients or those without defined syndromes or genetic conditions. Teratologic hip dislocations usually have identifiable causes, such as arthrogryposis or a genetic syndrome, and occur before birth.

**ETIOLOGY AND RISK FACTORS**

Although the etiology remains unknown, the final common pathway in the development of DDH is increased laxity of the joint, which fails to maintain a stable femoroacetabular articulation. This increased laxity is probably the result of a combination of hormonal, mechanical, and genetic factors. A positive family history for DDH is found in 12-33% of affected patients. DDH is more common among female patients (80%), which is thought to be because of the greater susceptibility of female fetuses to maternal hormones such as relaxin, which increases ligamentous laxity. Although only 2-3% of all babies are born...
in breech presentation, the incidence of DDH in these patients is 16-25%.

Any condition that leads to a tighter intrauterine space and, consequently, less room for normal fetal motion may be associated with DDH. These conditions include oligohydramnios, large birth weight, and 1st pregnancy. The high rate of association of DDH with other intrauterine molding abnormalities, such as torticollis and metatarsus adductus, supports the theory that the crowding phenomenon has a role in the pathogenesis. The left hip is the most commonly affected; in the most common fetal position, this is the hip that is usually forced into adduction by the mother’s sacrum.

**Epidemiology**

Although most newborn screening studies suggest that some degree of hip instability can be detected in 1 in 100 to 1 in 250 babies, actual dislocated or dislocatable hips are much less common, being found in 1-1.5 of 1,000 live births.

There is marked geographic and racial variation in the incidence of DDH. The reported incidence based on geography ranges from 1.7 in 1,000 babies in Sweden to 75 in 1,000 in Yugoslavia to 188.5 in 1,000 in a district in Manitoba, Canada. The incidence of DDH in Chinese and African newborns is almost 0%, whereas it is 1% for hip dysplasia and 0.1% for hip dislocation in white newborns. These differences may be the result of environmental factors, such as child-rearing practices, rather than to genetic predisposition. African and Asian caregivers have traditionally carried babies against their bodies in a shawl so that a child’s hips are flexed, abducted, and free to move. This keeps the hips in the optimal position for stability and for dynamic molding of the developing acetabulum by the cartilaginous femoral head. Children in Native American and Eastern European cultures, which have a relatively high incidence of DDH, have historically been swaddled in confining clothes that bring their hips into extension. This position increases the tension of the psoas muscle-tendon unit and might predispose the hips to displace and eventually dislocate laterally and superiorly.

**Pathoanatomy**

In DDH, several secondary anatomic changes can develop that can prevent reduction. Both the fatty tissue in the depths of the socket, known as the pulvinar, and the ligamentum teres can hypertrophy, blocking reduction of the femoral head. The transverse acetabular ligament usually thickens as well, which effectively narrows the opening of the acetabulum. In addition, the shortened iliopectineus tendon becomes taut across the front of the hip, creating an hourglass shape to the hip capsule, which limits access to the acetabulum. Over time, the dislocated femoral head places pressure on the acetabular rim and labrum, causing the labrum to infold and become thick.

The shape of a normal femoral head and acetabulum depends on a concentric reduction between the two. The more time that a hip spends dislocated, the more likely that the acetabulum will develop abnormally. Without a femoral head to provide a template, the acetabulum will become progressively shallow, with an oblique acetabular roof and a thickened medial wall.

**Clinical Findings**

**The Neonate**

DDH in the neonate is asymptomatic and must be screened for by specific maneuvers. Physical examination must be carried out with the infant unclothed and placed supine in a warm, comfortable setting on a flat examination table.

The Barlow provocative maneuver assesses the potential for dislocation of a nondisplaced hip. The examiner adducts the flexed hip and gently pushes the thigh posteriorly in an effort to dislocate the femoral head (Fig. 678-2). In a positive test, the hip is felt to slide out of the acetabulum. As the examiner relaxes the proximal push, the hip can be felt to slip back into the acetabulum.

The Ortolani test is the reverse of Barlow test: The examiner attempts to reduce a dislocated hip (Fig. 678-3). The examiner grasps the child’s thigh between the thumb and index finger and, with the 4th and 5th fingers, lifts the greater trochanter while simultaneously abducting the hip. When the test is positive, the femoral head will slip into the socket with a delicate clunk that is palpable but usually not audible. It should be a gentle, nonforced maneuver.

A hip click is the high-pitched sensation (or sound) felt at the very end of abduction during testing for DDH with Barlow and Ortolani maneuvers. Classically, a hip click is differentiated from a hip clunk, which is felt as the hip goes in and out of joint. Hip clicks usually originate in the ligamentum teres or occasionally in the fascia lata or psoas tendon and do not indicate a significant hip abnormality.

**The Infant**

As the baby enters the 2nd and 3rd mo of life, the soft tissues begin to tighten and the Ortolani and Barlow tests are no longer reliable. In this age group, the examiner must look for other specific physical findings, including limited hip abduction, apparent shortening of the thigh, proximal location of the greater trochanter, asymmetry of the gluteal...
The Walking Child

The walking child often presents to the physician after the family has noticed a limp, a waddling gait, or a leg-length discrepancy. The affected side appears shorter than the normal extremity, and the child toe-walks on the affected side. The Trendelenburg sign is positive in these children, and an abductor lurch is usually observed when the child walks. As in the younger child, there is limited hip abduction on the affected side and the knees are at different levels when the hips are flexed (the Galeazzi sign). Excessive lordosis, which develops secondary to altered hip mechanics, is common and is often the presenting complaint.

DIAGNOSTIC TESTING

Ultrasongraphy

Because it is superior to radiographs for evaluating cartilaginous structures, ultrasonography is the diagnostic modality of choice for DDH before the appearance of the femoral head ossific nucleus (4-6 mo). During the early newborn period (0-4 wk), however, physical examination is preferred over ultrasonography because there is a high incidence of false-positive sonograms in this age group. In addition to elucidating the static relationship of the femur to the acetabulum, ultrasonography provides dynamic information about the stability of the hip joint. The ultrasound examination can be used to monitor acetabular development, particularly of infants in Pavlik harness treatment; this method can minimize the number of radiographs taken and might allow the clinician to detect failure of treatment earlier.

In the Graf technique, the transducer is placed over the greater trochanter, which allows visualization of the ilium, the bony acetabulum, the labrum, and the femoral epiphysis (Fig. 678-7). The angle formed by the line of the ilium and a line tangential to the boney roof of the acetabulum is termed the \(\alpha\) angle and represents the depth of the acetabulum. Values >60 degrees are considered normal, and those <60 degrees imply acetabular dysplasia. The \(\beta\) angle is formed by a line drawn tangential to the labrum and the line of the ilium; this represents the cartilaginous roof of the acetabulum. A normal \(\beta\) angle is <55 degrees; as the femoral head subluxates, the \(\beta\) angle increases. Another useful test is to evaluate the position of the center of the head compared to the vertical line of the ilium. If the line of the ilium falls lateral to the center of the head, the epiphysis is considered reduced. If the line falls medial to the center of the head, the epiphysis is uncovered and is either subluxated or dislocated.

Screening for DDH with ultrasound remains controversial. Although routinely performed in Europe, meta-analyses indicate that data are insufficient to give clear recommendations. In the United States, the current recommendations are that every newborn undergo a clinical examination for hip instability. Children who have findings suspicious for DDH should be followed up with ultrasound. Most authors agree that infants with risk factors for DDH (breech position, family history, torticollis) should be screened with ultrasound regardless of the clinical findings.

Radiography

Radiographs are recommended for an infant once the proximal femoral epiphysis ossifies, usually by 4-6 mo. In infants of this age, radiographs have proved to be more effective, less costly, and less operator dependent than an ultrasound examination. An anteroposterior (AP) view of the pelvis can be interpreted with the aid of several classic lines drawn on it (Fig. 678-8).
The goals in the management of DDH are to obtain and maintain a concentric reduction of the femoral head within the acetabulum in order to provide the optimal environment for the normal development of both the femoral head and acetabulum. The later the diagnosis of DDH is made, the more difficult it is to achieve these goals, the less potential there is for acetabular and proximal femoral remodeling, and the more complex the required treatments.

**Newborns and Infants Younger Than 6 Months**

Newborns hips that are Barlow-positive (reduced but dislocatable) or Ortolani-positive (dislocated but reducible) should generally be treated with a Pavlik harness as soon as the diagnosis is made. The management of newborns with dysplasia who are younger than 4 wk of age is less clear. A significant proportion of these hips normalize within 3-4 wk; consequently, many physicians prefer to reexamine these newborns after a few weeks before making treatment decisions. A study of 128 newborns with mildly dysplastic hips based on the results of an ultrasound (alpha angles between 43 and 50 degrees) who were randomly assigned to receive immediate abduction splinting or active sonographic surveillance from birth with Frejka splinting provided if treatment was subsequently needed revealed no difference in radiologic findings at 6 yr of age.

**Hilgenreiner's line** is a horizontal line drawn through the top of both triradiate cartilages (the clear area in the depth of the acetabulum). **Perkins line** is a vertical line through the most lateral ossified margin of the roof of the acetabulum, drawn perpendicular to Hilgenreiner's line. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these 2 lines. **Shenton's line** is a curved line drawn from the medial aspect of the femoral neck to the lower border of the superior pubic ramus. In a child with normal hips, this line is a continuous contour. In a child with hip subluxation or dislocation, this line consists of 2 separate arcs and is described as "broken."

The **acetabular index** is the angle formed between Hilgenreiner's line and a line drawn from the depth of the acetabular socket to the most lateral ossified margin of the roof of the acetabulum. In the newborn, the acetabular index can be up to 40 degrees; by 4 mo in the normal infant, it should be no more than 30 degrees. In the older child, the **center-edge angle** is a useful measure of femoral head coverage. This angle is formed at the juncture of the Perkins line and a line connecting the lateral margin of the acetabulum to the center of the femoral head. In children 6-13 yr old, an angle >19 degrees is normal, whereas in children 14 yr and older, an angle >25 degrees is considered normal.

**TREATMENT**

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Triple diapers or abduction diapers have no place in the treatment of DDH in the newborn; they are usually ineffective and give the family a false sense of security. Acetabular dysplasia, subluxation, or dislocation can all be readily managed with the Pavlik harness. Although other braces are available (von Rosen splint, Frejka pillow), the Pavlik harness remains the most commonly used device worldwide (Fig. 678-9). By maintaining the Ortolani-positive hip in a Pavlik harness on a full-time basis for 6 wk, hip instability resolves in 95% of cases. After 6 mo of age, the failure rate for the Pavlik harness is >50% because it is difficult to maintain the increasingly active and crawling child in the harness. Frequent examinations and readjustments are necessary to ensure that the harness is fitting correctly. The anterior straps of the harness should be set to maintain the hips in flexion (usually ~90-100 degrees); excessive flexion is discouraged because of the risk of femoral nerve palsy. The posterior straps are designed to encourage abduction. These are generally set to allow adduction just to neutral, as forced abduction by the harness can lead to avascular necrosis of the femoral epiphysis.

If follow-up examinations and ultrasounds do not demonstrate concentric reduction of the hip after 3-4 wk of Pavlik harness treatment, the harness should be abandoned. Continued use of the harness beyond this period in a persistently dislocated hip can cause Pavlik harness disease, or wearing away of the posterior aspect of the acetabulum, which can make the ultimate reduction less stable.

**Children 6 Months to 2 Years of Age**

The principal goals in the treatment of late-diagnosed dysplasia are to obtain and maintain reduction of the hip without damaging the femoral head. Closed reductions are performed in the operating room under general anesthesia. The hip is moved to determine the range of motion in which it remains reduced. This is compared to the maximal range of motion to construct a “safe zone” (Fig. 678-10). An arthrogram obtained at the time of reduction is very helpful for evaluating the depth and stability of the reduction (Fig. 678-11). The reduction is maintained in a well-molded spica cast, with the “human position” of moderate flexion and abduction being the preferred position. After the procedure, single-cut CT or MRI may be used to confirm the reduction. Twelve weeks after closed reduction, the plaster cast is removed; an abduction orthosis is often used at this point to encourage further remodeling of the acetabulum. Failure to obtain a stable hip with a closed reduction indicates the need for an open reduction. In patients younger than 2 yr of age, a secondary acetabular or femoral procedure is rarely required. The potential for acetabular development after closed or open reduction is excellent and continues for 4-8 yr after the procedure.

**Children Older Than 2 Years**

Children 2-6 yr of age with a hip dislocation usually require an open reduction. In this age group, a concomitant femoral shortening osteotomy is often performed to reduce the pressure on the proximal femur and minimize the risk of osteonecrosis. Because the potential for acetabular development is markedly diminished in these older children, a pelvic osteotomy is usually performed in conjunction with the open reduction. Postoperatively, patients are immobilized in a spica cast for 6-12 wk.

**COMPLICATIONS**

The most important complication of DDH is avascular necrosis of the femoral epiphysis. Reduction of the femoral head under pressure or in extreme abduction can result in occlusion of the epiphyseal vessels and produce either partial or total infarction of the epiphysis. Revascularization soon follows, but if the physis is severely damaged, abnormal growth and development can occur. The hip is most vulnerable to this complication before 4-6 mo, when the ossific nucleus appears. Management, as previously outlined, is designed to minimize this complication. With appropriate treatment, the incidence of avascular necrosis for DDH is reduced to 5-15%. Other complications in DDH include redislocation, residual subluxation, acetabular dysplasia, and postoperative complications, including wound infections.

*Bibliography is available at Expert Consult.*
Bibliography


678.2 Transient Monoarticular Synovitis (Toxic Synovitis)
Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Transient synovitis (toxic synovitis) is a reactive arthritis and is one of the most common causes of hip pain in young children.

ETIOLOGY
The cause of transient synovitis remains unknown. It has been variously described as a nonspecific inflammatory condition or as a post-viral immunologic synovitis because it tends to follow recent viral illnesses.

CLINICAL MANIFESTATIONS
Although transient synovitis can occur in all age groups, it is most prevalent in children between 3 and 8 yr of age, with a mean onset at age 6 yr. Approximately 70% of all affected children have had a nonspecific upper respiratory tract infection 7-14 days before the onset of symptoms. Symptoms often develop acutely and usually consist of pain in the groin, anterior thigh, or knee, which may be referred from the hip. These children are usually able to bear weight on the affected limb and typically walk with a painful, limp gait. The hip is not held flexed, abducted, or laterally rotated unless a significant effusion is present. They are often afebrile or have a low-grade fever <38°C (100.4°F).

DIAGNOSIS
Transient synovitis is a clinical diagnosis, but laboratory and radiographic tests can be useful to rule out other more serious conditions. In transient synovitis, infection labs (erythrocyte sedimentation rate, serum C-reactive protein, and white blood cell counts) are relatively normal, but on occasion a mild elevation in the erythrocyte sedimentation rate is observed. AP and Lauenstein (frogleg) lateral radiographs of the pelvis may be acquired and are also usually found to be normal. Ultrasonography of the hip is preferred to x-rays and often demonstrates a joint effusion.

The most important condition to exclude before confirming a diagnosis of toxic synovitis is septic arthritis. Children with septic arthritis usually appear more systemically ill than those with transient synovitis. The pain associated with septic arthritis is more severe, and children often refuse to walk or move their hip at all. High fever, refusal to walk, and elevations of the erythrocyte sedimentation rate, serum C-reactive protein, and white blood cell count all point toward a diagnosis of septic arthritis. If the clinical scenario is suspicious for septic arthritis, an ultrasound-guided aspiration of the hip joint should be performed to make the definitive diagnosis (see Chapter 685). An exception to these criteria is hip septic arthritis due to Kingella kingae, which may have minimal inflammation and low grade or no fever (see Chapter 685). MRI may be needed to detect an associated osteomyelitis.

TREATMENT
The treatment of transient monoarticular synovitis of the hip is symptomatic. Recommended therapies include activity limitation and relief of weight bearing until the pain subsides. Antiinflammatory agents and analgesics can shorten the duration of pain. Most children recover completely within 3-6 wk.

Bibliography is available at Expert Consult.

678.3 Legg-Calvé-Perthes Disease
Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Legg-Calvé-Perthes disease (LCPD) is a hip disorder of unknown etiology that results from temporary interruption of the blood supply to the proximal femoral epiphysis, leading to osteonecrosis and femoral head deformity.

ETIOLOGY
Although the underlying etiology remains obscure, most authors agree that the final common pathway in the development of LCPD is disruption of the vascular supply to the femoral epiphysis, which results in ischemia and osteonecrosis. Infection, trauma, and transient synovitis have all been proposed as causative factors but are unsubstantiated. Factors leading to thrombophilia, an increased tendency to develop thrombosis and hypofibrinolysis, and a reduced ability to lyse thrombi have been identified. Factor V Leiden mutation, deficiency of proteins C and S, lupus anticoagulant, antiphospholipid antibodies, antithrombin, and plasminogen activator might play a role in the abnormal clotting mechanism. These abnormalities in the clotting cascade are thought to increase blood viscosity and the risk for venous thrombosis. Poor venous outflow leads to increased intraosseous pressure, which, in turn, impedes arterial inflow, causing ischemia and cell death.

EPIDEMIOLOGY
The incidence of LCPD in the United States is 1 in 1,200 children with boys 4-5 times more likely to be affected than girls. The peak incidence of the disease is between the ages of 4 and 8 yr. Bilateral involvement is seen in approximately 10% of the patients, but the hips are usually in different stages of collapse. East Asians have the lowest incidence of the disease and whites the highest.

PATHOGENESIS
Early pathologic changes in the femoral head are the result of ischemia and necrosis; subsequent changes result from the repair process. The disease course may have 4 stages, although variations have been described. The initial stage of the disease, which often lasts 6 mo, is characterized by synovitis, joint irritability, and early necrosis of the femoral head. Revascularization then leads to osteoclastic-mediated resorption of the necrotic segment. The necrotic bone is replaced by fibrovascular tissue rather than new bone, which compromises the structural integrity of the femoral epiphysis. The second stage is the fragmentation stage, which typically lasts 8 mo. During this stage, the femoral epiphysis begins to collapse, usually laterally, and begins to extrude from the acetabulum. The healing stage, which lasts approximately 4 yr, begins with new bone formation in the subchondral region. Reossification begins centrally and expands in all directions. The degree of femoral head deformity depends on the severity of collapse and the amount of remodeling that occurs. The final stage is the residual stage, which begins after the entire head has reossified. A mild amount of remodeling of the femoral head still occurs until the child reaches skeletal maturity. LCPD often damages the proximal femoral physis leading to a short neck (coxa breva) and trochanteric overgrowth.

CLINICAL MANIFESTATIONS
The most common presenting symptom is a limp of varying duration. Pain, if present, is usually activity related and may be localized in the groin or referred to the anteromedial thigh or knee region. Failure to recognize that thigh or knee pain in a child may be secondary to hip pathology can cause further delay in the diagnosis. Less commonly, the onset of the disease may be much more acute and may be associated with a failure to ambulate. Antalgic gait (a limp characterized by a shortening of gait phase on the injured side to alleviate weight-bearing pain) may be particularly prominent after strenuous activity at the end of the day. Hip motion, primarily internal rotation and abduction, is limited. Early in the course of the disease, the limited abduction is secondary to synovitis and muscle spasm in the adductor group; however, with time and the subsequent deformities that can develop, the limitation of abduction can become permanent. A mild hip flexion contracture of 10-20 degrees may be present. Atrophy of the muscles of the thigh, calf, or buttock from disuse secondary to pain may be evident. An apparent leg-length inequality may be caused by an adduction contracture or true shortening on the involved side from femoral head collapse.
Bibliography


DIAGNOSIS
Routine plain radiographs are the primary diagnostic tool for LCPD. AP and Lauenstein (frogleg) lateral views are used to diagnose, stage, provide prognosis for, and follow the course of the disease (Fig. 678-12). It is important when evaluating disease progression that all radiographs be viewed sequentially and compared with previous radiographs to assess the stage of the disease and determine the true extent of epiphyseal involvement.

In the initial stage of LCPD, the radiographic changes include a decreased size of the ossification center, lateralization of the femoral head with widening of the medial joint space, a subchondral fracture, and physeal irregularity. In the fragmentation stage, the epiphysis appears fragmented, and there are scattered areas of increased radio- lucency and radiodensity. During the reossification stage, the bone density returns to normal by new (woven) bone formation. The residual stage is marked by the reossification of the femoral head, gradual remodeling of head shape until skeletal maturity, and remodeling of the acetabulum.

In addition to these radiographic changes, several classic radiographic signs have been reported that describe a “head at risk” for severe deformity. Lateral extrusion of the epiphysis, a horizontal physis, calcification lateral to the epiphysis, subluxation of the hip, and a radiolucent horizontal V in the lateral aspect of the physis (Gage’s sign) are all associated with a poor prognosis.

In the absence of changes on plain radiographs, particularly in the early stages of the disease, MRI is useful to diagnose early infarction and determine the degree of impaired perfusion. During the remodeling or residual stages, MRI is extremely helpful to define the abnormal anatomy and determine the extent of intra-articular injury. Arthrography can be useful to dynamically assess the shape of the femoral head, demonstrate whether a hip can be contained, and diagnose hinge abduction. Table 678-1 outlines the differential diagnosis.

CLASSIFICATION
Catterall proposed a 4-group classification based on the amount of femoral epiphysis involvement and a set of radiographic “head at-risk” signs. Group I hips have anterior femoral head involvement of 25%, no sequestrum (an island of dead bone within the epiphysis), and no metaphyseal abnormalities. Group II hips have up to 50% involvement and a clear demarcation between involved and uninvolved segments. Metaphyseal cysts may be present. Group III hips display up to 75% involvement and a large sequestrum. In group IV, the entire femoral head is involved. Use of the Catterall classification system has been limited because of a high degree of interobserver variability.

The Herring lateral pillar classification is the most widely used radiographic classification system for determining treatment and prognosis during the active stage of the disease (Fig. 678-13). Unlike the Catterall system, the Herring classification has a high degree of interobserver reliability. Classification is based on several radiographs taken during the early fragmentation stage. The lateral pillar classification system for LCPD evaluates the shape of the femoral head epiphysis on AP radiograph of the hip. The head is divided into 3 sections or pillars. The lateral pillar occupies the lateral 15-30% of the head width, the central pillar is approximately 50% of the head width, and the medial pillar is 20-35% of the head width. The degree of involvement of the lateral pillar can be subdivided into 3 groups. In group A, the lateral pillar is radiographically normal. In group B, the lateral pillar has some lucency but >50% of the lateral pillar height is maintained. In group C, the lateral pillar is more lucent than in group B and <50% of the pillar height remains. Herring has added a B/C border group to the classification system.

### Table 678-1: Differential Diagnosis of Legg-Calvé-Perthes Disease

<table>
<thead>
<tr>
<th>OTHER CAUSES OF AVASCULAR NECROSIS</th>
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<tr>
<td>Sickle cell disease</td>
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<td>Other hemoglobinopathies (e.g., thalassemia)</td>
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<td>Chronic myelogenous leukemia</td>
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<td>Steroid medication</td>
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<td>Sequela of traumatic hip dislocation</td>
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<td>Treatment of developmental dysplasia of the hip</td>
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<td>Septic arthritis</td>
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**Figure 678-12 A**, Anteroposterior radiograph of the pelvis shows epiphyseal fragmentation in the right hip, characteristic of the fragmentation phase of Legg-Calvé-Perthes disease. **B**, The frogleg lateral view demonstrates subchondral fracture, increased density of the femoral head, and some collapse.

**Figure 678-13** Lateral pillar classification for Legg-Calvé-Perthes disease. **A**, There is no involvement of the lateral pillar. **B**, More than 50% of the lateral pillar height is maintained. **C**, Less than 50% of the lateral pillar height is maintained.
classification system to describe patients with approximately 50% collapse of the lateral pillar.

**NATURAL HISTORY AND PROGNOSIS**

Children who develop signs and symptoms of LCPD before the age of 6 yr tend to recover with fewer residual problems. Patients older than 9 yr of age at presentation usually have a poor prognosis. The reason for this difference is that the remodeling potential of the femoral head is higher in younger children. Greater extent of femoral head involvement and duration of the disease process are additional factors associated with a poor prognosis. Hips classified as Catterall groups III and IV and lateral pillar group C generally have a poor prognosis.

**TREATMENT**

The goal of treatment in LCPD is preservation of a spherical, well-covered femoral head and maintenance of hip range of motion that is close to normal. Although the treatment of LCPD remains controversial, most authors agree that the general approach to these patients should be guided by the principle of containment. This principle is predicated on the fact that while the femoral head is fragmenting, and therefore in a softened condition, it is best to contain it entirely within the acetabulum; by doing so, the acetabulum acts as a mold for the regenerating femoral head. Conversely, failure to contain the head permits it to deform, with resulting extrusion and impingement on the lateral edge of the acetabulum. To be successful, containment must be instituted early while the femoral head is still moldable; once the head has healed, repositioning the femoral epiphysis will not aid remodeling and can, in fact, worsen symptoms.

Initial options to manage symptoms include activity limitation, protected weightbearing, and nonsteroidal antiinflammatory medications. “Nonoperative” containment can be achieved by using a Petrie cast to restore abduction and to direct the femoral head deeper into the acetabulum. Petrie casts are 2 long-leg casts that are connected by a bar and can be helpful to keep the hips in abduction and internal rotation (the best position for containment). Casting is generally done in conjunction with an arthrogram to confirm containment and a tenotomy (molded femoral head) acts as a mold for the regenerating femoral head. Conversely, failure to contain the head permits it to deform, with resulting extrusion and impingement on the lateral edge of the acetabulum. To be successful, containment must be instituted early while the femoral head is still moldable; once the head has healed, repositioning the femoral epiphysis will not aid remodeling and can, in fact, worsen symptoms.

Surgical containment may be approached from the femoral side, the acetabular side, or both sides of the hip joint. A varus osteotomy of the proximal femur is the most common procedure. Pelvic osteotomies in LCPD are divided into 3 categories: acetabular rotational osteotomies, shelf procedures, and medial displacement or Chiari osteotomies. Any of these procedures can be combined with a proximal femoral varus osteotomy when severe deformity of the femoral head cannot be contained by a pelvic osteotomy alone.

After healing of the epiphysis, surgical treatment shifts from containment to managing the residual deformity. Patients with hinge abduction or joint incongruity might benefit from a valgus-producing proximal femoral osteotomy. Coxa breva and overgrowth of the greater trochanter can be managed by performing an advancement of the trochanter. This helps restore the length–tension relationship of the abductor mechanism and can alleviate abductor fatigue. Patients with femoroacetabular impingement from irregularity of the femoral head can often be helped with an osteoplasty or cheilectomy of the offending prominence.

**CLASSIFICATION**

SCFEs may be classified temporally, according to onset of symptoms (acute, chronic, acute-on-chronic); functionally, according to patient’s ability to bear weight (stable or unstable); or morphologically, as the extent of displacement of the femoral epiphysis relative to the neck (mild, moderate, or severe), as estimated by measurement on radiographic or CT images.

An *acute* SCFE is characterized as one occurring in a patient who has prodromal symptoms for >3 wk with a sudden exacerbation of pain. Radiographs demonstrate femoral neck remodeling and further displacement of the capital epiphysis beyond the remodeling point of the femoral neck.

The stability classification separates patients based on their ability to ambulate and is more useful in predicting prognosis and establishing a treatment plan. The SCFE is considered *stable* when the child is able to walk with or without crutches. A child with an *unstable* SCFE is unable to walk with or without walking aids. Patients with unstable SCFE have a much higher prevalence of osteonecrosis (up to 50%) compared to those with stable SCFE (nearly 0%). This is most likely because of the vascular injury caused at the time of initial displacement.

SCFE may also be categorized by the degree of displacement of the epiphysis on the femoral neck. The head-shaft angle difference is <30 degrees in mild slips, between 30 and 60 degrees in moderate slips, and >60 degrees in severe slips, compared to the normal contralateral side.

**ETIOLOGY AND PATHOGENESIS**

SCFEs are most likely caused by a combination of mechanical and endocrine factors. The plane of cleavage in most SCFEs occurs through the hypertrophic zone of the physis. During normal puberty, the physis becomes more vertically oriented, which converts mechanical forces from compression to shear. In addition, the hypertrophic zone becomes elongated in pubertal adolescents due to high levels of circulating hormones. This widening of the physis decreases the threshold for mechanical failure. Normal ossification depends on a number of different factors, including thyroid hormone, vitamin D, and calcium. Consequently, it is not surprising that SCFEs occur with increased incidence in children with medical disorders such as hypothyroidism, hypopituitarism, and renal osteodystrophy. Obesity, one of the largest risk factors for SCFE, affects both the mechanical load on the physis and the level of circulating hormones. The combination of mechanical and endocrine factors results in gradual failure of the physis, which allows posterior and inferior displacement of the head in relation to the femoral neck.

**EPIDEMIOLOGY**

The annual incidence of SCFE is 2 per 100,000 in the general population. Incidence has ranged from 0.2 per 100,000 in eastern Japan to 10.08 per 100,000 in the northeastern United States. The African-American and Polynesian populations are reported to have an increased incidence of SCFE. Obesity is the most closely associated risk factor in the development of SCFE; approximately 65% of the patients are >90th percentile in weight-for-age profiles. There is a predilection for boys to

Bibliography is available at Expert Consult.

**678.4 Slipped Capital Femoral Epiphysis**

_Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans_

Slipped femoral capital epiphysis (SCFE) is a hip disorder that affects adolescents, most often between 10 and 16 yr of age, and involves failure of the physis and displacement of the femoral head relative to the neck.
Bibliography
be affected more often than girls and for the left hip to be affected more often than the right. Bilateral involvement has been reported in as many as 60% of cases, nearly half of which may be present at the time of initial presentation.

**CLINICAL MANIFESTATIONS**

The classic patient presenting with a SCFE is an obese, African-American boy between the ages of 11 and 16 yr. Girls present earlier, usually between 10 and 14 yr of age. Patients with chronic and stable SCFEs tend to present after weeks to months of symptoms. Patients usually limp to some degree and have an externally rotated lower extremity. Physical examination of the affected hip reveals a restriction of internal rotation, abduction, and flexion. Commonly, the examiner notes that as the affected hip is flexed, the thigh tends to rotate progressively into more external rotation with increased flexion (Fig. 678-14). Most patients complain of groin symptoms, but isolated thigh pain or knee pain is a common presentation from referred pain along the course of the obturator nerve. Missed or delayed diagnosis often occurs in children who present with knee pain and do not receive appropriate imaging of the hip. Patients with unstable SCFEs usually present in an urgent fashion. Children typically refuse to allow any range of motion of the hip; much like a hip fracture, the extremity is shortened, abducted, and externally rotated.

**DIAGNOSTIC STUDIES**

AP and frogleg lateral radiographic views of both hips are usually the only imaging studies needed to make the diagnosis. Because approximately 25% of patients have a contralateral slip on initial presentation, it is critical that both hips be carefully evaluated by the treating physician. Radiographic findings include widening and irregularity of the physis, a decrease in epiphyseal height in the center of the acetabulum, a crescent-shaped area of increased density in the proximal portion of the femoral neck, and the "blanch sign of Steel" corresponding to the double density created from the anteriorly displaced femoral neck overlying the femoral head. In an unaffected patient, Klein's line, a straight line drawn along the superior cortex of the femoral neck on the AP radiograph, should intersect some portion of the lateral capital femoral epiphysis. With progressive displacement of the epiphysis, Klein's line no longer intersects the epiphysis (Fig. 678-15). Although some of these radiographic findings can be subtle, most diagnoses can be readily made on the frogleg lateral view, which reveals the characteristic posterior and inferior displacement of the epiphysis in relation to the femoral neck (Fig. 678-16).

**TREATMENT**

Once the diagnosis is made, the patient should be admitted to the hospital immediately and placed on bed rest. Allowing the child to go home without definitive treatment increases the risk that a stable SCFE will become an unstable SCFE and that further displacement will occur. Children with atypical presentations (younger than 10 yr of age, thin body habitus) should have screening labs sent to rule out an underlying endocrinopathy.

The goal of treatment is to prevent further progression of the slip and to stabilize (i.e., close) the physis. Although various forms of treatment have been used in the past, including spica casting, the current gold standard for the treatment of SCFE is in situ pinning with a single, large screw (Fig. 678-17). The term in situ implies that no attempt is made to reduce the displacement between the epiphysis and femoral neck because doing so increases the risk of osteonecrosis. Screws are typically placed percutaneously under fluoroscopic guidance. Postoperatively, most patients are allowed partial weight bearing with crutches for 4-6 wk, followed by a gradual return to normal activities. Patients should be monitored with serial radiographs to be sure that the physis is closing and that the slip is stable. After healing from the initial stabilization, patients with severe residual deformity may be candidates for proximal femoral osteotomy to correct the deformity, reduce impingement, and improve range of motion.

Because 20-40% of children will develop a contralateral SCFE at some point, many orthopedists advocate prophylactic pin fixation of the contralateral (normal) side in patients with a unilateral SCFE. The benefits of preventing a possible slip must be balanced with the risks of performing a potentially unnecessary surgery. Several recent studies have attempted to analyze decision models for prophylactic pinning, but controversy remains regarding the optimal course of treatment.

**COMPLICATIONS**

Osteonecrosis and chondrolysis are the 2 most serious complications of SCFE. Osteonecrosis, or avascular necrosis, usually occurs as a result of injury to the retinacular vessels. This can be caused by an initial force of injury, particularly in unstable slips, forced manipulation of an acute or unstable SCFE, compression from intracapsular hematoma, or as a direct injury during surgery. Partial forms of osteonecrosis can also appear following internal fixation; this can be caused by a disruption of the intraepiphyseal blood vessels. Chondrolysis, on the other
Radiographic appearance of slipped capital femoral epiphysis (SCFE) on presentation. A, Appearance of acute SCFE on a frogleg lateral view. The displacement of the epiphysis is suggestive of a Salter-Harris type I fracture of the upper femoral physis. There are no secondary adaptive changes noted in the femoral neck. B, Frogleg lateral radiographs in a patient with many months of thigh discomfort and a chronic slipped epiphysis. Adaptive changes in the femoral neck predominate, and the epiphysis is centered on the adapted femoral neck. C, Frogleg lateral radiographs of a patient with acute-on-chronic SCFE. The patient had several months of vague thigh pain, with sudden, severe exacerbation of that pain. The acute displacement of the epiphysis is evident. Unlike in acute SCFE (see A), secondary adaptive remodeling changes are also present in the femoral neck, beyond which the epiphysis has acutely displaced. (From Herring JA: Slipped capital femoral epiphysis. In Herring JA, editor: Tachdjian’s pediatric orthopaedics, ed 5, Philadelphia, 2014, WB Saunders, Fig. 18-1, p. 632.)

Preoperative (A) and postoperative (B) radiographs demonstrating the in situ pinning in a case of slipped capital femoral epiphysis.

hand, is an acute dissolution of articular cartilage in the hip. There are no clear causes of this complication, but it is believed to be associated with more-severe slips, to occur more commonly among African-Americans and girls, and to be associated with pins or screws protruding out of the femoral head.

_Bibliography is available at Expert Consult._
Bibliography
Abnormalities of the spine can result from a variety of causes including congenital, developmental, and traumatic. In addition to spinal deformities, back pain has become increasingly prevalent in childhood and adolescence, and a thoughtful diagnostic evaluation is required to establish the diagnosis while minimizing the overutilization of healthcare resources. The most common deformities are scoliosis and kyphosis. An early diagnosis is important, as a subset of patients may be candidates for “preventive” strategies such as bracing. Early intervention may potentially reduce the number requiring surgery, or at least reduce the magnitude or risks if surgical treatment is required.

Scoliosis may be from congenital bony deformities, may be idiopathic, including infantile, juvenile, or adolescent idiopathic scoliosis, or may be associated with a variety of underlying conditions, including neuromuscular diseases, connective tissue diseases, and genetic
syndromes (Table 679-1). The pediatrician is often the first to diagnose these conditions. A familiarity with the physical examination, as well as the natural history and treatment options, will help the pediatrician to not only establish an early diagnosis but also to provide basic counseling for the patient and family regarding the diagnosis, general prognosis, and whether any referral and/or further workup might be indicated.

While parents and families are primarily concerned about the resulting cosmetic abnormalities, the physician diagnosing a patient with a spine deformity must carefully consider both the potential for underlying causes requiring treatment and the patient's long-term prognosis. If a certain curve magnitude is crossed in a patient with adolescent idiopathic scoliosis, the curve will be likely to continue to progress in adulthood and may require surgical treatment. Progressive curvatures in the neuromuscular population may result in respiratory insufficiency in addition to a loss of sitting balance. Additionally, while the majority of patients with excessive thoracic kyphosis have benign flexible curves and require no active treatment, a subset will have a progressive or rigid deformity which may require treatment. Parents and the patient must have an understanding of the deformity, how it may progress, and potential complications associated with the diagnosis. Table 679-1 presents a classification of common spinal abnormalities.

### NORMAL SPINAL CURVATURES

The spine has curvatures that are anatomically normal in the lateral (sagittal) plane. Cervical lordosis (convex anteriorly), thoracic kyphosis (convex posteriorly), and lumbar lordosis regions are biomechanically advantageous as they maintain relationships of the body relative to the forces of gravity, which is important for balance. These curvatures also help to conserve energy by minimizing the amount of muscular activity required to maintain an upright posture.

Abnormalities affecting these normal curvatures, termed sagittal plane imbalances, can be measured on a sagittal spine radiograph. A vertical line, or plumb line, drawn from the center of the 7th cervical vertebra should normally fall through the posterosuperior corner of the sacrum. Disorders affecting sagittal alignment include thoracic hyperkyphosis and lumbar hyperlordosis. Although scoliosis is a 3-dimensional deformity, it is most commonly described as a lateral curvature of the spine in the frontal (coronal) plane.

### Table 679-1 Classification of Spinal Deformities

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<td>Spino-cerebellar degeneration (Friedreich ataxia, Charcot-Marie-Tooth disease)</td>
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<tr>
<td>Spinal cord trauma</td>
<td>Lower motor neuron</td>
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<td>Polymyelitis</td>
<td>Spinal muscular atrophy</td>
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| Myopathies | Duchenne muscular dystrophy |
|           | Anthrogrypsis |
|           | Other muscular dystrophies |
| Syndromes | Neurorhabdomyelosis |
|           | Marfan syndrome |
|           | Compensatory |
| KYPHOSIS  | Postural kyphosis (flexible) |
|           | Scheuermann disease |
|           | Congenital kyphosis |
|           | Failure of formation |
|           | Failure of segmentation |
| Mixed     |                          |


### 679.1 Idiopathic Scoliosis

**R. Justin Mistovich and David A. Spiegel**

**DEFINITION**

The word *scoliosis* takes its origin from the Greek word *skolios*, meaning bent or curved. Medically recognized for centuries, Hippocrates described scoliosis in his treatise *On Articulations*. Scoliosis is a complex 3-dimensional spinal deformity that is defined in the coronal plane as a curve of at least 10 degrees, measured by the Cobb method, on a posteroanterior (PA) radiograph of the spine. The deformity also includes rotation of the vertebrae and also malalignment in the sagittal plane, such as a segmental apical lordosis in thoracic curves.

**ETIOLOGY**

The etiology of idiopathic scoliosis remains unknown; it is likely that the cause is multifactorial with genetic, hormonal, cellular, anatomic, and functional contributions.

A genetic link has been proposed with sex-linked dominant, autosomal dominant and polygenic inheritance patterns all suggested. Genetic involvement has been substantiated in studies of twins, demonstrating a 73% concordance rate for adolescent idiopathic scoliosis (AIS) in monozygotic twins compared to a 36% concordance rate in dizygotic twins.

AIS is 2-10 times more common in females than males. Investigators have attempted to explain this difference as a genetic effect: It has been hypothesized that males are not as susceptible to the involved genes as females. Therefore, affected males must inherit a larger number of susceptibility genes to have a scoliosis phenotype. Males would pass more susceptibility genes onto their children and would therefore have more affected children. This polygenic prediction is known as the Carter effect; fathers with AIS transmit the disease to 80% of their children, but mothers with AIS transmit the disease to only 56% of their children.

Certain polymorphisms in the estrogen receptor gene are linked to an increased curve progression and higher risk of requiring operative treatment. Genetic analysis may also be able to determine curve progression, although data concerning the effectiveness and validity of this are limited.

Endocrine factors may have a possible role in the disease pathology. Lower plasma melatonin levels have been noted in patients with progressive curvatures. Abnormal levels of growth hormone and insulin-like growth factor-1 have also been discovered. Leptin, the hormone responsible for satiety, is found at lower levels in patients with AIS.

Cellular structures may be involved in the disease process. Calmodulin, a regulator of the contractile properties of muscle, occurs at increased levels in the platelets of patients with progressive AIS.

MRI studies of the brain in patients with AIS have found that the cerebellum of affected patients is hypertrophied in areas involving the somatosensory tracts, motor control, and response to visual stimulation. These areas of hypertrophy may be a compensation for impaired balance resulting from malalignment of the spine. Other studies have noted a decrease in regional brain volumes and white matter in the corpus callosum and internal capsule between patients affected with AIS and normal adolescents. Girls with AIS have also been noted to have a larger foramen magnum. The importance of these imaging findings remains unclear.

Functional evaluations of patients with AIS have noted abnormalities in proprioception, postural balance, somatosensory function, somatosensory evoked potentials and electromyography. Patients with AIS have differences in vestibular-evoked myogenic potentials, suggesting that otoith system dysfunction may play a role in the disease. Approximately one-third of girls with AIS have osteopenia on dual-energy x-ray absorptiometry studies, and of these, 80% will have lifelong osteopenia. Osteopenia is linked to an increased risk of curve
scoliosis is rare, comprising 0.5-4% of all cases of idiopathic scoliosis. Other symptoms, such as osteoid osteoma or spinal cord tumor (see Chapter 679.5 on bone tumors), must carefully be excluded.

**CLASSIFICATION OF IDIOPATHIC SCOLIOSIS**

Idiopathic scoliosis is classified according to the age at onset. **Infantile scoliosis** is rare, comprising 0.5-4% of all cases of idiopathic scoliosis. It describes patients with spinal curves noted from birth to 3 yr of age. **Juvenile scoliosis** accounts for 8-16% of cases of idiopathic scoliosis and affects children age 3-10 yr. **AIS** affects patients 11 yr of age and older, and comprises 70-80% of all cases of idiopathic scoliosis.

**CLINICAL PRESENTATION OF IDIOPATHIC SCOLIOSIS**

When evaluating a patient with a structural spinal curvature, a thorough history and physical examination are required because idiopathic scoliosis is a diagnosis of exclusion. All other potential causes, including congenital bone malformations, neuromuscular and connective tissue diseases, and tumors, must carefully be excluded.

Patients often present after a positive screening by their primary care physician, through a school screening program, or because they (or their family or friends) have noticed a cosmetic deformity. It should be noted that school screening programs have become controversial, as some authors claim that the programs do not change the outcomes of patients requiring intervention, result in unnecessary physician visits and radiographs, and are not cost-effective. The British Orthopaedic Association and the U.S. Preventive Services Task Force have both issued statements recommending against routine screening for the above reasons. However, citing the need for early identification of scoliosis to reduce the risk of operative complications common to correction of large, neglected curves, the Scoliosis Research Society, an international organization of spine surgeons, still advocates for school screening.

Back pain is not commonly a primary presenting complaint of patients with scoliosis, although when questioned, one-third of adolescents with idiopathic scoliosis will endorse some degree of back discomfort at some point in time. To keep this finding in perspective, approximately 35% of healthy adolescents complain of episodes of low back pain and discomfort. However, if a patient presents with the complaint of significant back pain associated with a curvature, the physician must perform a careful physical exam, check spinal radiographs, and evaluate for other causes of pain, including spondylolysis, spondylolisthesis, tethered cords or a syrinx, herniated discs, or tumors such as osteoid osteoma or spinal cord tumor (see Chapter 679.5 below).

**PHYSICAL EXAMINATION OF IDIOPATHIC SCOLIOSIS**

Evaluate the patient in the standing position, from both the front and the side, to identify any asymmetry in the chest wall, trunk, and/or shoulders.

Begin the examination focusing on the back. The earliest abnormality noted on physical exam in patients with scoliosis is asymmetry of the posterior chest wall on forward bending. This test, called the Adams forward-bending test (Fig. 679-1) is performed by placing a scoliometer at the apex of the deformity with the patient bending 45 degrees forward. An inclination measuring 7 degrees or more has been suggested as the cut off for orthopaedic referral. Scoliosis is a 3-dimensional deformity. Patients develop a posterior rib hump on the convex side of the spinal curve as a result of the rotational component of the deformity. The anterior chest wall may be prominent on the concavity of the curve as a result of outward rib rotation. Other associated findings may include elevation of the shoulder, a lateral shift of the trunk, or an apparent leg-length discrepancy. A lumbar curve may also compensate for a primary limb-length discrepancy, with the apex toward the shorter leg.

Next, examine the patient from the side to evaluate the degree of kyphosis and lordosis. The upper thoracic spine normally has a smooth, gently rounded kyphotic curve with an apex in the midthoracic region. The cervical spine and lower lumbar spine have concave, or lordotic curves. The magnitude of these sagittal contours varies both with age and among individuals of the same age. Children have less cervical lordosis and more lumbar lordosis than do adults or adolescents. When examining a patient with idiopathic scoliosis, a common finding is a loss of the normal thoracic kyphosis, resulting in what is called a relative thoracic lordosis. A common benign finding in normal adolescent thoracic spines is a flexible roundback, or postural kyphosis. This can be corrected voluntarily when the patient extends his or her spine. This is different from sharp, abrupt, or accentuated forward angulation in the thoracic or thoracolumbar region, which is indicative of a pathologic kyphotic deformity.

The final exam component is a careful neurologic examination, as scoliosis may be associated with an underlying neurologic diagnosis. Check superficial abdominal reflexes, extremity reflexes, muscle strength, and examine for clonus. A high suspicion is necessary in patients with infantile and juvenile idiopathic scoliosis because 20% have an associated intraspinal abnormality such as a tethered spinal cord or syringomyelia. The index of suspicion for neurologic involvement is further raised in the presence of back pain or neurologic symptoms, café-au-lait spots, a sacral dimple, midline cutaneous

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**Figure 679-1 Structural changes in idiopathic scoliosis. A, As curvature increases, alterations in body configuration develop in both the primary and compensatory curve regions. B, Asymmetry of shoulder height, waistline, and elbow-to-flank distance are common findings. C, Vertebral rotation and associated posterior displacement of the ribs on the convex side of the curve are responsible for the characteristic deformity of the chest wall in scoliosis patients. D, In the school screening examination for scoliosis, the patient bends forward at the waist. Rib asymmetry of even a small degree is obvious. (From Scoles PV: Spinal deformity in childhood and adolescence. In Behrman RE, Vaughn VC III, editors: Nelson textbook of pediatrics, update 5, Philadelphia, 1989, WB Saunders.)**
abnormalities such as a hair patch or skin tag, or a unilateral foot deformity.

**RADIOPHGRAPHIC EVALUATION OF IDIOPATHIC SCOLIOSIS**

Standing, high-quality, PA and lateral radiographs of the entire spine are recommended at the initial evaluation for patients with clinical findings suggestive of a spinal deformity. On the PA radiograph, the degree of curvature is determined by the Cobb method, in which the angle between the superior and inferior vertebrae tilted into the curve is measured (Fig. 679-2). A line is drawn across the superior end plate of each end vertebra, and the angle between perpendicular lines drawn from each of these is measured.

Spinal MRI is indicated when there is suspicion of an underlying cause for the scoliosis, such as spinal cord abnormality based on age (infantile or juvenile curves), abnormal findings on the history and physical examination, and atypical radiographic features. Atypical radiographic findings may include certain curve patterns such as a left thoracic curve, double thoracic curves, or high thoracic curves. Other radiographic abnormalities include widening of the spinal canal and erosive or dysplastic changes in the vertebral body or ribs. On the lateral radiograph, an increase in thoracic kyphosis or an absence of segmental lordosis may be suggestive of an underlying neurologic abnormality.

**NATURAL HISTORY OF IDIOPATHIC SCOLIOSIS**

The decision to treat the patient is based on the natural history of idiopathic scoliosis. Uniquely, infantile idiopathic scoliosis may spontaneously resolve in 20-90% of cases. Patients with infantile scoliosis who have developmental delay, curves presenting after 1 yr of age, and larger magnitude curves are more likely to progress. A radiographic parameter called the Mehta angle can also be used to predict curve progression. This measurement examines the vertebra at the apex of the thoracic curve. It measures the angle formed by a line perpendicular from the vertebral end plate and a line down the center of the rib. The measurement is calculated on the convex and concave side, and the final rib vertebral angle difference is calculated by subtracting the convex side from the concave side. A curve with an rib vertebral angle difference <20 degrees will resolve in approximately 80% of cases, whereas a curve with an rib vertebral angle difference >20 degrees will progress in more than 80% of cases. Curves that resolve typically do so before 2 yr of age.

Several factors affect the rate of curve progression in patients with AIS. Curves are more likely to progress in patients with significant growth remaining and skeletal immaturity, meaning that the growth plates, or physes, remain open allowing for continued skeletal growth. Findings associated with significant growth remaining are younger age, premenarchal status, Tanner stage I or II, and Risser sign (a radiographic measurement of ossification of the iliac crest) of 0 or 1. Other factors affecting progression are the curve magnitude, pattern, and patient gender. There is a relationship between curve progression and 3-dimensional spinal measurements of vertebral wedging, axial rotation, and torsion, possibly allowing for better prognostication of curves at risk. In general, female patients are more likely than males to have curves that progress. Younger, premenarchal girls with curves between 20 degrees and 30 degrees have a significantly higher risk of progression than do girls 2 yr after menarche with similar curves, demonstrating the significance of age on progression. The older group is unlikely to have any progression at all while premenarchal girls with the same curve are likely to progress. Thoracic curves <30 degrees rarely progress after skeletal maturity, whereas those >45-50 degrees may progress approximately 1 degree per year through life.

Functionally, there are not many significant, clinically detrimental effects of smaller curves. Idiopathic thoracic curvatures greater than 60-70 degrees may be associated with abnormalities on pulmonary function testing, and curves of higher magnitude may cause clinically significant cardiopulmonary impairment and even cor pulmonale in severe curves. Long-term studies demonstrate that a degree of chronic back pain may be a problem for patients with scoliosis, although there is no definitive connection between pain and the curve magnitude or location. Furthermore, nearly 70% of patients with pain reported low or moderate severity of symptoms, stating that the pain does not interfere with normal activities.
TREATMENT OF IDIOPATHIC SCOLIOSIS

Brace treatment may prevent curve progression in a significant number of patients with AIS and is most successful when an early diagnosis is established. The success rate depends upon the amount of growth remaining; patients with infantile or juvenile scoliosis are much more likely to require a surgical procedure than those with AIS. Adherence with the recommended protocol for wearing the brace will influence the outcome. Although various schedules for brace wear have been reported, from 12-23 hr daily, the brace is generally worn for 16 or more hours per day, maximizing wear when the patient is upright. Adherence can be a challenge in the adolescent population. Braces are offered for treatment of skeletally immature patients with curves >30 degrees at the first visit, or in patients who are being followed and have developed progression of their curvature beyond 25 degrees. Bracing is ineffective in curvatures >45 degrees. The brace is worn until cessation of growth in males, but in females some authors will consider weaning from the brace when the patient is more than 1.5 yr postmenarchal, is a Risser 4 or greater and/or has grown less than 1 cm over the previous 6 mo.

Surgical treatment involves spinal arthrodesis or fusion and is usually recommended for skeletally immature patients with progressive curves >45 degrees and skeletally mature patients with curves >50 degrees. The goals of surgery are to arrest progression of the deformity, to improve cosmesis, and to achieve a balanced spine, all while minimizing the number of vertebral segments that are stabilized.

Implants, including pedicle screws, sublaminar wires, and hooks, are attached to 2 longitudinal rods (Fig. 679-3). These are used to apply mechanical forces to the spine, correcting the deformity in both the frontal and lateral planes. The spine is decorticated and bone graft is placed for the fusion portion of the procedure. Correction also maintains normal frontal and sagittal spinal balance. The strength of the spinal implants maintains correction without requiring a postoperative brace in the majority of cases.

Most procedures are performed posteriorly using pedicle screw fixation, which affords excellent correction, especially of the rotational component of the deformity. Posterior osteotomies are often added to enhance flexibility and improve the degree of correction in stiffer curves. Anterior spinal releases requiring a thoracotomy are performed infrequently. Open anterior thoracic and thoracolumbar procedures violate the chest wall and often the diaphragm, and pulmonary function may take up to 2 yr to return to normal values. Even though thoracoscopic techniques can be utilized to perform anterior spinal release with or without instrumentation and fusion, their use is limited.

Patients with conditions such as neurofibromatosis (see Chapter 596.1) and myelomeningocele (see Chapter 591.4) have a higher likelihood of achieving a non-union of their fusion, and an anterior fusion is considered in addition to the posterior fusion in these groups. Younger patients, in whom the triradiate cartilage remain open, are at risk for crankshaft, or progressive deformity/loss of correction as a consequence of continued anterior spinal growth, after a posterior fusion. Traditionally, these patients were treated by simultaneous anterior fusion to remove the growth potential; however, the rigidity of constructs with pedicle screws negates the need for this additional surgery. For idiopathic thoracolumbar and lumbar curves, an anterior fusion with instrumentation can be considered, although the posterior approach with osteotomies and pedicle screw fixation is being used more frequently to avoid the need for anterior surgery. Posterior spinal fusion has been associated with accelerated degeneration of the unfused levels. In many, this remains asymptomatic, but the long-term effects remain unknown.

Several emerging techniques are being evaluated in the management of idiopathic scoliosis. These include new approaches to the spine, attempts to preserve remaining growth in younger patients, and even specialized treatments to save the lives of young patients with curves so significant that they result in mortality secondary to inadequate pulmonary volume. There are techniques to correct curves without limiting future growth and even to modulate spinal growth and prevent future fusion surgeries. The FDA-approved VEPTR (vertical expandable prosthetic titanium rib) helps young children with thoracic insufficiency syndrome caused by severe spinal curves with restrictive lung disease, often associated with a high mortality rate (see Chapter 679.2 below). The chest wall device can enlarge the thorax and correct scoliosis without adverse effect to somatic growth, likely triggering lung growth. After implantation, it is lengthened twice a year by minor surgery. Long-term survival rates are favorable for these extremely severe scoliosis patients treated by VEPTR. The device obtains and maintains correction without fusing the spine, which allows for alveolar development and maximizes trunk height prior to definitive spinal fusion.

Growing rods have also been used in young children with scoliosis. These devices have fixation points placed at the proximal and distal ends of the deformity, with expandable rods placed subcutaneously, spanning the length of the deformity. Similar to the VEPTR, growing rods require additional minor operations to lengthen the rods twice a year until skeletal maturity or definitive spinal fusion.

Intervertebral stapling is an experimental technique that attempts to dynamically modify spinal growth in immature individuals with smaller curves. Staples are placed through either an open or thorascopic approach across the intervertebral disk space (growth zone) on the convex side of the curve. This technique holds the spine in a corrected position and limits growth on the convex side, preventing further curvature, and achieving correction through concave growth. It remains to be seen whether this technique will play a role in the management of patients with idiopathic scoliosis.

Bibliography is available at Expert Consult.
Bibliography
Intraspinal anomalies are identified in approximately 15-40% of patients. Spinal dysraphism is the general term applied to such lesions (see Chapters 591 and 606). Examples include diastematomyelia, split-cord malformations, intraspinal lipomas, arachnoid cysts, teratomas, dermoid sinuses, fibrous bands, and tight filum terminale. Cutaneous findings that may be seen in patients with closed spinal dysraphism include hair patches, skin tags or dimples, sinuses, and hemangiomas. Infants with these cutaneous abnormalities overlying the spine may benefit from ultrasonography to rule out an occult spinal dysraphic condition. MRI is indicated in infants, but in the past was delayed in older patients until a clinical indication is present, such as tethering of the spinal cord, which may present as back or leg pain, calf atrophy, progressive unilateral foot deformity (especially cavovarus), and problems with bowel or bladder function.

**CLASSIFICATION OF CONGENITAL SCOLIOSIS**

Congenital scoliosis is classified by the type of developmental abnormality: either a failure of formation or a failure of segmentation. The deformities are then further described by the anatomic features of the affected vertebra. Failures of formation result in wedge vertebrae or hemivertebrae. Failures of segmentation result in unilateral bars vertebral or block vertebrae. Lastly, some instances of congenital scoliosis result from a combination of both failure of formation and failure of segmentation (Fig. 679-4). One or more bony anomalies may occur in isolation or in combination.

**NATURAL HISTORY OF CONGENITAL SCOLIOSIS**

The risk of progression depends on the growth potential of each anomaly, which may vary considerably. Close radiographic follow-up is required. Progression of these curves is most pronounced during periods of rapid growth associated with the 1st 2-3 yr of life and during the adolescent growth spurt.
It should be noted that surgery in these young, syndromic patients is not without risk. One recent study found a complication rate of nearly 85% and a mortality rate of >15% in patients who underwent operative treatment for all types of early onset scoliosis, including those with congenital scoliosis as well as other associated syndromes producing early onset scoliosis.

**THORACIC INSUFFICIENCY SYNDROME**

When multiple levels of the thoracic spine are involved in the presence of fused ribs, a progressive 3-dimensional deformity of the chest wall may impair lung development and function. This development is termed thoracic insufficiency syndrome. As a result of thoracic insufficiency syndrome, the chest wall cannot support normal respiration resulting in decreased life expectancy.

Thoracic insufficiency syndrome may be seen in patients with several recognized conditions such as Jarcho-Levin syndrome (spondylocostal or spondylothoracic dysplasia; see Chapter 108) and Jeune syndrome (asphyxiating thoracic dystrophy; see Chapter 417.3), as well as patients with severe spinal deformities. These difficult cases are being treated with a technique called expansion thoracoplasty, in which the thoracic cage is gradually expanded over time by progressive lengthening of the chest wall on the concavity of the spinal deformity (or in some cases on both sides of the spine). The procedure involves an opening wedge thoracostomy, followed by placement of a vertical expandable titanium prosthetic rib. The implant is then lengthened at regular intervals (Fig. 679-5). The primary goal is to gradually correct the chest wall deformity to improve pulmonary function, and a secondary goal is correction of an associated spinal deformity. This technique is currently not approved by the FDA for the treatment of scoliosis in the absence of a thoracic insufficiency, and further study will help to refine and possible expand the indications for this new technique.

**Bibliography is available at Expert Consult.**

The anatomic characteristics of the malformed vertebra play a significant role in the progression of deformity. The most severe form of congenital scoliosis is a unilateral unsegmented bar with a contralateral hemivertebra. In this anomaly, the spine is fused the side of the unsegmented bar but also has a growth center on the other side at the location of the hemivertebra at the same level. This combination of deformities in the bony spine results in a rapidly progressive curve. As a result, all affected patients usually require surgical stabilization. A unilateral unsegmented bar is also associated with significant progression and in most cases will require surgical intervention. An isolated hemivertebra must be followed closely, and many, but not all, of these will be associated with a progressive deformity that requires surgical intervention. In contrast, an isolated block vertebra has little growth potential and rarely requires treatment.

**TREATMENT OF CONGENITAL SCOLIOSIS**

Early diagnosis and prompt treatment of progressive curves are essential. Bracing is not indicated for most congenital curves because of their structural nature, except in rare cases to treat additional curves not associated with the congenital abnormality. The treatment of progressive curves is spinal fusion, or arthrodesis. Once a bony abnormality is identified that is likely to progress, surgery is performed before progression occurs, preventing development or further inevitable progression of spinal deformity. If the deformity has already developed, surgical correction is difficult to achieve and the risk of neurologic complications is high.

Both anterior and posterior spinal fusion is often required. Other procedures that are employed in selected patients include an isolated posterior spinal fusion. A convex hemiepiphysiodesis can be performed with certain deformities, fusing only 1 side of the spine to allow some correction of the deformity by permitting growth on the noninvolved side of the curve. Complete excision of a hemivertebra, along with fusion of a short segment of the spine, can be performed via a posterior approach and may result in better correction and spinal balance in selected cases.
Bibliography
679.3 Neuromuscular Scoliosis, Genetic Syndromes, and Compensatory Scoliosis
R. Justin Mistovich and David A. Spiegel

NEUROMUSCULAR SCOLIOSIS
Scoliosis is frequently identified in children with neuromuscular diseases such as cerebral palsy, muscular dystrophies and other myopathies, spinal muscular atrophy, Friedreich ataxia, myelomeningocele, polio, and arthrogryposis. Children with spinal cord injuries are also at high risk for a progressive curvature. The etiology and natural history of these patients differ from idiopathic and congenital scoliosis. Most cases result from weakness and/or imbalance of the trunk musculature. Spasticity may also contribute to spinal curvatures. In some cases, such as myelomeningocele, coexisting congenital vertebral anomalies may be present, further contributing to curve development.

As might be expected, neuromuscular scoliosis is most common in patients with higher degrees of neurologic impairment, usually those who are nonambulatory and may not have adequate control of their trunk. It is diagnosed in more than 70% of nonambulatory patients with cerebral palsy (see Chapter 598.1), and in more than 90% of patients with Duchenne muscular dystrophy (see Chapter 609.1).

The diagnosis is suspected on physical examination. In nonambulators, the most common curve pattern is a C-shaped thoracolumbar or lumbar curve (Fig. 679-6). This curve is typically associated with pelvic obliquity. In contrast, ambulatory patients with diagnoses such as Friedreich ataxia may have curve patterns more similar to idiopathic scoliosis.

In ambulatory patients, the examination is similar to the previously described physical examination for idiopathic scoliosis. In nonambulators, the back is inspected with the patient sitting upright. Any asymmetry should be noted. These patients often need manual support to maintain an upright position. If any progressive asymmetry is observed, then sitting PA and lateral radiographs are obtained. Because prophylactic treatment cannot alter the natural history of the disease, it is appropriate to establish the diagnosis clinically and obtain radiographs if the curve is noted to progress.

The clinical course of patients with neuromuscular scoliosis depends on the severity of neuromuscular involvement as well as the nature of the underlying disease process. Progressive diseases are often associated with progressive curvatures. The consequences of a progressive scoliosis in the neuromuscular population involve both function, especially sitting and standing balance, as well ease of hygiene and personal care. Pulmonary dysfunction may be expected with the gradual deformation of the rib cage and vertebral–pelvic axis, as well as collapse of the spine with the pelvis impinging on the rib cage. Diaphragmatic function is impaired, and changes in chest volume and chest wall architecture will undoubtedly exacerbate the pulmonary dysfunction owing to underlying muscle weakness. Pulmonary function may be difficult to document in some patient populations, especially those with severe cerebral palsy. Additionally, patients who initially were marginal ambulators may lose the ability to walk altogether as their scoliosis advances. Curves associated with pelvic obliquity result in asymmetric seating pressures, which may limit sitting endurance and may rarely cause skin breakdown and decubitus ulcers. Patients may also experience pain from impingement of the rib cage on the iliac crest.

The treatment of neuromuscular scoliosis depends on the age of the patient, the underlying diagnosis, and the magnitude of the deformity. The goal is to achieve or maintain a straight spine over a level pelvis, especially in patients who are wheelchair bound, and to intervene early before curve magnitude and rigidity become severe. In contrast to idiopathic and congenital scoliosis, neuromuscular curves often continue to progress after skeletal maturity. In general, curves of greater than 40–50 degrees will continue to worsen over time. Brace treatment does not affect the natural history of neuromuscular scoliosis, and standard braces used for idiopathic scoliosis are poorly tolerated in neuromuscular patients. A soft spinal orthosis may improve sitting balance and ease of care, although it does not prevent progression of the curvature.

In general, a spinal arthrodesis is offered to patients with progressive curves >40–50 degrees. The indications will differ somewhat based on the underlying diagnosis. For example, patients with Duchenne muscular dystrophy are offered surgery when their curves progress beyond 20–30 degrees, thereby having surgery before the anticipated decline in pulmonary or cardiac function preclude their ability to tolerate it. Ambulatory patients with curvatures similar to those seen in idiopathic scoliosis are managed by similar principles. Patients who are nonambulatory with pelvic obliquity are usually managed by a spinal fusion extending from the upper thoracic spine to the pelvis, similar to that described in the idiopathic scoliosis section. A brace is not required following this procedure. Treatment decisions must be individualized in those nonambulatory patients with spastic quadriplegia, and are based on loss of function, the potential to improve hygiene or personal care, and the desires of the family and/or caregivers.

Although complications are relatively frequent in comparison with patients with nonneuromuscular curves, the available literature suggests that most patients benefit in terms of function and ease of care. To better identify patients at risk of complications, a recent study found that nonambulatory patients and those with curves 60 degrees or greater had a significantly increased risk of postoperative major complications, including ileus, pneumonia, infection, and wound problems. Because of the risks involved and potential for complications, this surgery should ideally be performed at centers with significant experience.

SYNDROMES AND GENETIC DISORDERS
Representative examples of this diverse group of diagnoses include neurofibromatosis, osteogenesis imperfecta, connective tissue diseases including Marfan syndrome (see Chapter 702), Ehlers-Danlos syndrome (see Chapter 659), and Prader-Willi syndrome (see Chapter 81), among many others. Patients with these diagnoses should have their spine examined routinely during visits to their primary care physician. Similar to other types of scoliosis, the follow-up and treatment are based on the age of the patient, the degree of deformity, whether progression has been documented, and the underlying diagnosis.

COMPENSATORY SCOLIOSIS
Leg-length inequality is a common clinical diagnosis and is usually associated with a small compensatory lumbar curvature (see Chapter...
679.4 Kyphosis (Round-Back)

R. Justin Mistovich and David A. Spiegel

The normal thoracic spine has 20-50 degrees of kyphosis as measured from T3 to T12. This is measured using the Cobb method on a standing lateral radiograph of the thoracolumbar spine. A thoracic kyphosis in excess of the normal range of values is termed hyperkyphosis. These patients may present with cosmetic concerns, back pain, or both. A flexible or postural kyphosis may be overcorrected voluntarily or with postural adjustment, whereas a rigid kyphosis cannot be corrected passively. Causes of rigid kyphosis include Scheuermann disease and congenital kyphosis, among others. Table 679-2 lists conditions associated with hyperkyphosis.

The evaluation and treatment depends on the underlying diagnosis, the degree of deformity and its flexibility, whether the deformity is progressive, and whether any symptoms are present.

FLEXIBLE KYPHOSIS (POSTURAL KYPHOSIS)

Postural kyphosis is a common cosmetic concern and is most often recognized by family and friends. Adolescents with postural kyphosis can correct the curvature voluntarily. A standing lateral radiograph will show an increase in kyphosis but no pathologic changes of the involved vertebrae. There is no evidence to suggest that postural kyphosis progresses to a structural deformity. Although mild aching discomfort is sometimes reported, there is no evidence that the conditions leads to long-term symptoms or alterations in function or quality of life. The mainstay of treatment is reassurance. Physical therapy can be considered for muscular discomfort, although there are no data to suggest that a permanent alteration in alignment can be maintained.

Neither bracing nor surgery plays a role in the management of this condition.

STRUCTURAL KYPHOSIS

Scheuermann Disease

Scheuermann disease is the most common form of structural hyperkyphosis and is defined by wedging of greater than 5 degrees of 3 or more consecutive vertebral bodies at the apex of the deformity on a lateral radiograph. In addition, the apex of the thoracic kyphosis is lower than expected. Other radiographic findings include irregularities of the vertebral end plates and Schmorl nodes, which are herniations of the vertebral disc into the surface of the vertebral body. The etiology remains unknown but most likely involves the influence of mechanical forces in a genetically susceptible individual. Histologic specimens taken from patients with Scheuermann disease show a disordered pattern of endochondral ossification. However, it remains unclear whether these findings are the primary result of a genetic or metabolic pathologic process, or simply the secondary result of mechanical overload. The reported incidence varies from 0.4-10%, affecting boys 3 times more frequently than girls.

Physical Exam and Clinical Manifestations

Examine the patient from the side. There is a hyperkyphosis of the thoracic spine typically associated with a sharp contour. The apex of the deformity will often be in the lower thoracic spine. Patients are unable to correct the deformity voluntarily. Pain is a relatively common complaint. It is typically mild and near the apex of the kyphosis. The symptoms are intermittent, rarely severe, and occasionally limit certain activities. Neurologic symptoms are uncommon.

Radiographic Evaluation

The standard imaging protocol includes standing PA and lateral radiographs (Fig. 679-7). A specific, standardized technique in which the
Bibliography


arms are folded across the chest is recommended for the lateral view. In addition to the diagnostic findings noted above, a mild scoliosis is commonly seen. Less frequently, a spondylolysis may be identified on the lateral radiograph.

Natural History
Treatment depends on the age of the patient, the degree of deformity, and whether any symptoms are present. As adolescents, patients with Scheuermann kyphosis may have more complaints of back pain compared to other adolescents, but this often improves after skeletal maturity. With regard to back pain, several studies have found no difference between Scheuermann patients and controls, whereas others have noted an increased incidence of constant back pain. Patients’ self-esteem, participation in activities of daily living and recreational activities, and level of education are not different than in the general population. Kyphotic deformities greater than 90 degrees are more likely to be aesthetically unacceptable, symptomatic, and progressive. Deformities in excess of 100 degrees may be associated with restrictive pulmonary dysfunction.

Treatment
Because there are few absolute guidelines for treatment, treatment decisions must be individualized. Skeletally immature patients with mild deformity may benefit from a hyperextension exercise program, but the effects of this strategy on pain relief and spinal alignment, or the natural history, remain unknown. Patients with more than 1 yr of growth remaining and a kyphosis of greater than 55-60 degrees may benefit from a bracing program. A Milwaukee brace, which extends up to the neck, is recommended for curves with an apex above T7, while curves with a lower apex often may be treated by a thoracolumbar orthosis. The brace should be worn for up to 23 hr daily. Consideration also may be given to a serial casting or stretching program to gain flexibility prior to instituting the brace program. The goal of the brace is to prevent progression. A permanent improvement in alignment is seen less frequently. Skeletally mature patients with little or no pain and acceptable cosmesis are not treated. A spinal fusion may be considered in the rare patient with progressive deformity >70-80 degrees who is dissatisfied with his or her cosmetic appearance or who has persistent back pain despite nonoperative measures. An instrumented posterior spinal fusion from the upper thoracic to the mid lumbar spine is commonly performed, with spinal osteotomies to promote shortening of the spine when correcting with compressive forces. Some surgeons have recommended an anterior spinal release (discectomies and fusion) in addition to the posterior spinal fusion; however, this procedure is performed less frequently because of the increased neurologic risks of this combined procedure as the spine is lengthened during the correction.

CONGENITAL KYPHOSIS
Congenital kyphosis results from congenital anomalies of the vertebral bodies. In an anterior failure of formation (type I), a portion of the vertebral body fails to form. A kyphosis is typically identified after birth, and there is a high risk of progression and neurologic dysfunction. Spinal cord dysfunction commonly results from compression at the apex of the deformity. The second type of congenital kyphosis involves an anterior failure of segmentation, in which 2 vertebrae are fused (type II). The posterior elements of the spine continue to grow but the anterior spine does not, resulting in a variably progressive kyphosis and a much lower risk of neurologic dysfunction. Patients must be followed closely, and treatment is required in a significant number of cases. Similar to congenital scoliosis, abnormalities of other organ systems should be ruled out.

The treatment depends on the type of malformation, the degree of deformity, and whether neurologic symptoms are present. Bracing is ineffective, and surgical treatment is the only option for progressive curves. Because the natural history is so poor for type I deformities, spinal fusion is usually performed shortly after the diagnosis is made. The surgical goals are to prevent or treat kyphotic deformities, avoid neurologic deterioration, while maximizing spinal growth to the extent possible. This usually involves some form of spinal fusion, which may include anterior and/or posterior components, with or without resection of the vertebral remnant, and spinal instrumentation. Ideally, only a short segment of the spine will be fused to try and maximize trunk height. Deformities caused by anterior failure of segmentation also require spinal stabilization in some cases, but progression is typically slower, and patients are often followed over years to determine whether surgical stabilization will be required.

Bibliography is available at Expert Consult.

679.5 Back Pain in Children
R. Justin Mistovich and David A. Spiegel

With a lifetime prevalence of >70%, only the common cold affects individuals more frequently than back pain. Back pain is a frequent complaint in the pediatric and adolescent patient, affecting approximately 35% of adolescents. Back pain may be a physical manifestation of psychosocial factors in adolescents, similar to adults. Traditionally, the pediatric patient presenting with back pain warranted an aggressive clinical evaluation as the probability of establishing a specific diagnosis was high. Recent literature suggests that the incidence of both pediatric and adolescent back pain is increasing, while the proportion of patients having a diagnosable pathology is decreasing. In fact, a recent large cohort found no diagnosable pathology in 76% of patients. These trends add further complexity to determining the proper approach to diagnosis and treatment. The differential diagnosis is extensive (Table 679-3). Given the potential for serious pathology, a complete history and careful physical exam must be performed on all patients presenting with back pain, with appropriate diagnostic follow-up of concerning findings.

CLINICAL EVALUATION
A full, careful history is very important. Identify the location, character, and duration of symptoms. Any history of acute trauma or repetitive physical activities should be sought. Identify patients with at-risk athletic pursuits, including football lineman and gymnasts, who have a high incidence of spondylolysis (see Chapter 679.6). Symptoms consistent with a neoplastic or infectious etiology include pain that is constant or unremitting, not relieved by rest, and wakes the patient from sleep. Fevers, chills, or constitutional symptoms of weight loss or malaise are additional red flags for infectious or neoplastic processes.

Symptoms of neurologic dysfunction must also be uncovered. Patients should be questioned about the presence of any radicular symptoms, gait disturbance, muscle weakness, alterations in sensation, and changes in bowel or bladder function.

The physical examination includes a complete musculoskeletal and neurologic assessment. The patient should be adequately undressed for the clinical exam. Inspect the patient from the back and the side, identifying any changes in alignment in the frontal or sagittal plane. Assess range of motion in flexion, extension, and lateral bending. Pain with extension suggests pathology within the posterior elements of the spine such as spondylolysis. Forward flexion will exacerbate pain linked to abnormalities of the anterior column of the spine (vertebral body or disc), such as a herniated disc or discitis. Younger children may be asked to pick up an object off the floor to assess spinal flexion.

Palpation will reveal any areas of point tenderness over the posterior elements or the muscles and identify muscle spasm.

As spinal pain may be referred, an abdominal examination should be performed, and a gynecologic evaluation should also be considered. Pathology at the sacroiliac joint may also mimic low back pain. This joint should be stressed by compression of the iliac wings or by external rotation at the hip (Faber test).

A careful neurologic examination should be performed, including manual muscle testing, sensation, proprioception, and reflexes. Examine for myelopathy by performing the Babinski test, assessing for hyperreflexia, and checking for sustained, or greater than 3 beats, of
Bibliography


Differential Diagnosis of Back Pain

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<th>Table 679-3</th>
<th>Differential Diagnosis of Back Pain</th>
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| **INFLAMMATORY/INFECTIOUS** | Diskitis  
Vertebral osteomyelitis (pyogenic, tuberculous)  
Spinal epidural abscess  
Pyelonephritis  
Pancreatitis  
Psoas abscess |
| **RHEUMATOLOGIC** | Psoriatic arthritis  
Ankylosing spondylitis  
Reiter syndrome  
Pauciarticular juvenile idiopathic arthritis |
| **TRAUMATIC (ACUTE VERSUS REPETITIVE)** | Hip–pelvic anomalies  
Overuse syndromes  
Ventral stress fractures |
| **NEOPLASTIC** | Vertebral tumors  
Benign  
Eosinophilic granuloma  
Ewing's sarcoma  
Ankylosing spondylitis  
Aneurysmal bone cyst  
Osteoid osteoma  
Osteosarcoma  
Osteoblastoma  
Scoliosis  
Vertebral stress fractures |
| **OTHER** | Intraabdominal or pelvic pathology  
Following lumbar puncture  
Conversion reaction  
Juvenile osteoporosis |

Findings Consistent with a Nonmechanical Etiology Warranting Further Evaluation

- History of trauma  
- Pain that wakes the patient from sleep  
- Constant pain unrelieved by rest  
- Constitutional or systemic symptoms of fevers, chills, malaise, weight loss  
- Any neurologic dysfunction including weakness, numbness, radicular pain, gait changes, or bowel and bladder changes  
- Abnormalities in spinal alignment  
- Bony tenderness to palpation or vertebral step-offs  
- Significant pain with provocative tests (spinal flexion or extension)  
- Positive straight-leg raise test for neurologic symptoms below the knee  
- Abnormal neurologic exam

clonus. The superficial abdominal reflex should be tested by gently stroking the skin on each of the four quadrants surrounding the umbilicus. Normally, the umbilicus will move toward the area stimulated. A normal examination includes symmetry in the response on both sides of the midline, even if the reflex cannot be elicited on either side. An abnormal test suggests the presence of a subtle abnormality of spinal cord function, most commonly syringomyelia. Perform a straight-leg raise test to check for nerve root tension caused by a herniated disk, slipped vertebral apophysis, or other pathology. This examination should reproduce any neurologic symptoms distal to the knee.

MEDICAL DECISION MAKING

A detailed history and physical exam are the most important components of the initial evaluation, and should focus on identifying red flags and differentiating between mechanical and nonmechanical back pain. Findings consistent with a nonmechanical etiology, warrant a more aggressive evaluation and/or prompt referral (Table 679-4).

Patients with mechanical back pain and symptoms that are activity-related and improve with rest are typically treated by rest or activity restrictions and nonnarcotic analgesics. Physical therapy for core strengthening can be considered. The patient is asked to return for a follow-up appointment after 4-6 wks. Plain radiographs are commonly obtained at the discretion of individual practitioners, although, if no red flags are present, consider delaying radiographs until the follow-up appointment because of the cumulative adverse effects of radiation exposure. Patients presenting with concerning findings or those who have not improved after 6 wk of conservative care are subject to further investigation.

RADIOGRAPHIC AND LABORATORY EVALUATION

When further workup is indicated, posteroanterior and lateral radiographs of the involved region of the spine are the initial images of choice. Some clinicians will also utilize oblique radiographs of the lumbar spine when spondylolysis is in the differential diagnosis. If plain radiographs are normal, advanced imaging modalities are considered including a 3-phase technetium bone scan, a bone scan with single-photon emission CT if spondylolysis is suspected, CT for viewing osseous detail, and MRI for viewing soft tissue and intraspinal detail. There are advantages and disadvantages with each, and no evidenced-based guidelines are available for the work-up or back pain in the pediatric population.

When systemic signs or constitutional symptoms are present, a complete blood cell count with differential, erythrocyte sedimentation rate, and C-reactive protein should be ordered. In certain cases, laboratory tests to evaluate for inflammatory diseases, such as juvenile idiopathic arthritis, seronegative spondyloarthropathies, and ankylosing spondylitis, are indicated.

Bibliography is available at Expert Consult.

**679.6 Spondylolysis and Spondylolisthesis**

R. Justin Mistovich and David A. Spiegel

Spondylolysis represents a defect in the pars interarticularis, the segment of bone connecting the superior and inferior articular facets in the vertebra. It is thought to result from repetitive hyperextension stresses, in which compressive forces are transmitted from the inferior articular facet of the superior vertebra to the pars interarticularis of the inferior vertebra. A stress fracture, unilateral or bilateral, may progress to a spondylolisthesis. In many cases, this stress fracture does not heal, resulting in a pseudarthrosis or false joint, and thereby allowing motion through this bony area where motion should not normally exist.

Spondylolysis is common in athletes who engage in repetitive spinal hyperextension, especially gymnasts, football interior lineman, weight lifters, and wrestlers. Approximately 4-8% of the entire pediatric population is affected, making it the most common cause of back pain in
Bibliography


adolescents when a diagnosis can be established. Patients with excessive lordosis in the lumbar spine may be predisposed to developing a spondylolysis, and a genetic component has also been suggested. The lesion is most common at L5, but it may be identified at upper lumbar levels as well.

Spondylolisthesis represents a forward slippage of 1 vertebra on another and is also identified in approximately 4-5% of the population. There are multiple causes of spondylolisthesis, including dysplastic/congenital, isthmic (from a pars stress fracture), traumatic, and neoplastic. In children and adolescents, the most common types are dysplastic and isthmic. Between 5% and 15% of patients with spondylolysis will develop spondylolysis.

Spondylolisthesis is assessed on a standing lateral radiograph of the lumbosacral junction according to (1) percentage of forward translation of 1 vertebra on the other, (2) rotation of the involved vertebrae in the sagittal plane (slip angle), and (3) relative position of the sacrum during upright posture. For example, a grade 1 slip of L5 on S1 has less than 25% of the width of the vertebral body of L5 translated anteriorly on S1. Similarly, grade 2 is 25-50%, grade 3 is 50-75%, grade 4 is 75-100%. Spondyloptosis, or grade 5, describes a complete displacement of 1 vertebral body on the level below. The slip angle, which demonstrates the degree to which the superior vertebra is flexed forward relative to the underlying vertebra, and the verticality of the sacrum, both have a significant effect on sagittal balance or relationship of the sagittal weightbearing axis to the body segments. Abnormalities in sagittal spinal balance may be associated with compensatory flexion of the knees during ambulation, hamstring spasm and/or contracture, and back pain.

**CLINICAL MANIFESTATIONS**

Spondylolysis may occasionally be asymptomatic and diagnosed incidentally on imaging obtained for other reasons. Usually though, it presents with mechanical low back pain that may radiate to the buttocks, with or without spasm of the hamstring muscles. Neurologic symptoms are rare in patients with spondylolysis. However, patients with spondylolisthesis may experience neurologic symptoms from compression of the nerve roots causing radiculopathy or even the surgical emergency of cauda equina in which bowel and bladder function is affected.

**PHYSICAL EXAM**

Patients with spondylolysis often have discomfort with spinal extension or hyperextension. Provocative testing may include keeping the spine extended for 10-20 seconds to see if back pain can be reproduced. There may be discomfort with palpation of the spinous process of the involved vertebra. Patients with higher grades of spondylolisthesis demonstrate loss of lumbar lordosis, flattening of the buttocks on visual inspection, and a vertical sacrum caused by posterior rotation of the pelvis. A step off may be palpated between the spinous processes of the involved vertebrae. Hamstring contracture is testing by measuring the popliteal angle. The hip is flexed to 90 degrees while fully extending the contralateral hip to level the pelvis. The knee is then passively extended, and the popliteal angle represents the angle between the thigh (vertical) and the lower leg axis. The involved spinous processes may be tender to palpation. A careful, complete neurologic examination is essential.

**RADIOGRAPHIC EVALUATION**

The initial evaluation of the lumbar region should include high-quality anteroposterior and lateral radiographs. Some authors also prefer to obtain oblique radiographs, which demonstrate the classic “Scotty dog” finding. One study suggests that a series of 4 views may not offer greater diagnostic accuracy than 2 views. Standing PA and lateral radiographs are obtained if findings suggestive of scoliosis or hyperkyphosis are also present (Figs. 679-8 and 679-9). In patients with normal plain films, a bone scan with single-photon emission CT may help to diagnose a spondylolysis during the earliest stage of a stress reaction, prior to the formation of a stress fracture or an established pseudarthrosis. A CT scan with thin cuts may provide additional information to establish the presence of a pars defect. MRI is indicated in the presence of signs or symptoms of cauda equina or nerve root involvement.

**TREATMENT**

The asymptomatic patient with spondylolysis requires no treatment. Patients with pain are treated initially by activity modification, physical therapy for core strengthening, and nonnarcotic analgesics. The use of a lumbosacral orthosis, which immobilizes the spine in slight flexion to decompress the posterior elements, may lead to a faster resolution of symptoms. This orthosis is typically worn for 3-4 mo. Participation

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**Figure 679-8** A, Normal spine at 9 mo of age. B, Spondylolysis in the L4 vertebra at 10 yr of age. (From Silverman FN, Kuhn JP: Essentials of Caffey’s pediatric x-ray diagnosis, Chicago, 1990, Year Book Medical Publishers, p. 94.)
Spondylitis, meaning inflammation of the vertebrae, is most commonly caused by infectious or autoimmune processes. Both diskitis and vertebral osteomyelitis are causes within the spectrum of infectious spondylitis. Most causes of infectious spondylitis result from hematogenous seeding of osteoarticular structures. Diskitis involves bacterial infection of the disc space and is generally seen in children younger than 5 yr of age. In contrast, vertebral osteomyelitis most often occurs in older children and adolescents and involves the vertebral body. Differences in anatomic location of the infectious focus relate to the vascular development of the spine. Patients in the younger age range have vascular channels between the vertebral end plate and the disc space, explaining the prevalence of discitis. In older children these channels have closed, and the infection remains in the vertebra causing osteomyelitis.

Staphylococcus aureus (see Chapter 181) is the most common organism causing spine infections. Other, less-common organisms include Kingella kingae, group A streptococcus, Bartonella henselae, Salmonella, and Escherichia coli. Blood cultures have a sensitivity of only 30%. Percutaneous or open biopsy of the disc space is positive only 50-85% of the time. The differential diagnosis must include tuberculosis of the spine.

**CLINICAL MANIFESTATIONS**

A high index of suspicion is required to establish the diagnosis of infectious spondylitis. Patients may experience back pain, abdominal pain, fever, or malaise. Fever is less common and may be present in only 30% of patients. Toddlers may develop a limp, or refuse to walk or sit. In an effort to reduce the pain associated with spinal motion, the child will hold the spine in a rigid position. There may also be paraspinal muscle spasm. Local point tenderness over the affected spinous process is common. There may be a list or leaning of the trunk when the patient is viewed from the front or back, and from the side there may be a loss of lumbar lordosis. Neurologic manifestations are rare and if present suggest that an epidural abscess may be present. The L3-4 or L4-5 spaces are most commonly affected in diskitis.

Spine flexion compresses the anterior elements of the spine and will elicit an increase in pain. Asking a child to pick up an object from the ground is a simple way to elicit this provocative test. Although the white blood count may remain normal, the erythrocyte sedimentation rate is elevated in 80% of cases, and the C-reactive protein is also elevated.

**RADIOGRAPHIC EVALUATION**

The earliest radiographic finding is loss of lumbar lordosis. The characteristic features on plain radiographs are disc space narrowing, or loss of disc height, and irregularity of the adjacent vertebral end plates. However, these findings do not develop until 2-3 wk after the onset of symptoms. The diagnosis may be established earlier using either a technetium bone scan or MRI, although MRI is the most sensitive and specific imaging to diagnose osteomyelitis and to identify abscesses and/or neural compression (Fig. 679.10).

**TREATMENT**

Once the diagnosis is suspected clinically, the treatment involves symptomatic care and empiric antistaphylococcal antibiotics. Blood cultures should be obtained prior to the administration of antibiotics. The antibiotic agent may be modified if blood cultures are positive. Symptomatic care includes rest and analgesics, and a spinal orthosis may also be considered. The typical antibiotic course is from 4-6 wk; conversion from intravenous to oral agents may be acceptable after several days of improvement of the clinical course. A CT-guided needle biopsy of the disc space is usually reserved for patients who do not respond to empiric antibiotics. Surgical treatment is rarely required, and indications include establishing the diagnosis in patients who fail to respond.
Bibliography

Bone and Joint Disorders

either direct mechanical compression and/or a local inflammatory response.

Slipped vertebral apophysis, also called a posterior ring apophysis separation, is caused by an injury and is only found in the skeletally immature. A small fragment of osseous or osteocartilagenous material from the posterior corner of the vertebral body avulses and may cause direct mechanical compression to the spinal cords and/or nerve roots, similar to a disc herniation. Both disc herniations and ring apophysis separations can cause back pain, radicular symptoms (nerve root compression or irritation), and/or spinal cord compression.

ETIOLOGY

The etiology remains unknown, but predisposing activities for both of these conditions include heavy lifting, repetitive axial loading activities, and occasionally traumatic injury such as a fall. Approximately 30-60% of patients with symptomatic herniated discs have a history of to empiric antibiotics, and in those in whom an abscess and/or neurologic involvement are identified.

Bibliography is available at Expert Consult.

679.8 Intervertebral Disc Herniation/Slipped Vertebral Apophysis

R. Justin Mistovich and David A. Spiegel

Intervertebral disc herniation is the result of a tear in the outer layer of the vertebral disc, called the annulus fibrosus, which then allows for protrusion of the inner nucleus pulposus. At times, a free fragment of disc can rupture and compress the nerve roots or spinal cord. Bulging of the annulus without rupture may also be observed, resulting in back pain and occasionally radicular symptoms. Symptoms are from

Figure 679-10 A 15 mo old girl with abnormal gait and concern for an intraspinal mass had discitis/osteomyelitis. Lateral spine radiographs demonstrate narrowing of the T12-L1 intervertebral disc space (arrow in A). An axial bone window from a noncontrast CT scan of the spine demonstrates irregularity to the vertebral end plates (arrows in B). A sagittal T2-weighted image (C), a sagittal fat-saturated T1-weighted postcontrast image (D), and an axial T1-weighted postcontrast image (E) of the thoracolumbar junction demonstrate loss of height of the T12-L1 intervertebral disc space with adjacent T2 prolongation of the adjacent endplates (arrows in C), with corresponding abnormal enhancement in the same regions (arrows in D), and surrounding mass-like soft-tissue enhancement (arrowheads in E). Note the thickening/elevation and enhancement of the posterior longitudinal ligament (arrowheads in D). (From Pollock AN, Henesch SM: Infections of the spine and spinal cord. In Cooley BD, editor: Caffey’s pediatric diagnostic imaging, ed 12, Philadelphia, 2013, WB Saunders, Fig. 44-6, p. 465.)
**Bibliography**


a trauma or sports-related injury. Other associations include preexisting disc degeneration, congenital malformation, and genetic or environmental factors. There is also a potential association between disc degeneration and the herpes virus, adding the possibility of an infectious etiology.

**CLINICAL MANIFESTATIONS**

Symptoms of intervertebral disc herniation or slipped vertebral apophyseal separations in adolescents are similar to adult herniated disc symptoms. The major complaint is back pain, present in nearly 90% of patients. More than 30% of patients complain of radicular symptoms, or radiating sciatic-type pain into the legs. The back pain is often made worse by coughing, a Valsalva maneuver, or sitting. Pain may be relieved by standing or back extension. Inquire about weight loss, fever, or other constitutional symptoms to rule out an infectious or neoplastic etiology.

On physical examination, both paraspinal muscle spasm and a generalized spinal stiffness are common. Patients may lean toward the unaffected side to increase the size of the affected neural foramen thereby partially relieving symptoms. This results in a reactive scoliosis, not a true spinal curve, which improves with symptom resolution. Although overt signs of neurologic involvement are absent in most patients, a positive straight-leg raise test, causing radicular pain to shoot down the affected leg, is usually present. Pain is also worsened by spinal flexion.

It is critical perform a full neurologic evaluation. Evaluate sensation to light touch, pinprick, and proprioception. Check muscle strength and reflexes. It is critical to evaluate for perineal numbness, or saddle anesthesia. This finding, combined with changes in bowel or bladder function, which is also critical to specifically discern in the history, is indicative of cauda equina syndrome, a surgical emergency in which the nerve roots at the caudal end of the spinal cord are compressed or damaged.

**RADIOGRAPHIC EVALUATION**

Radiographs often show loss of lumbar lordosis, which is a result of muscle spasm, and sometimes a mild lumbar scoliosis. Other radiographic findings include degenerative changes and a loss of intervertebral disc height. MRI is the best study to establish the diagnosis of a disc herniation. CT is especially helpful to visualize a partially ossified fragment associated with a slipped apophysis.

**TREATMENT**

The initial treatment is nonoperative in the vast majority of patients—even if symptoms or findings of radiculopathy are observed. Treatment focuses on rest, activity modification, nonsteroidal antiinflammatory drugs, and physical therapy. An orthosis may provide additional symptomatic relief. Complete bed rest is not recommended. Epidural steroid injection may be discussed with patients after approximately 6 wk of treatment if symptoms persist; evidence suggests faster short-term pain relief but no difference in long-term outcome. However, if patients elect to undergo an epidural steroid injection, they should only have a single injection, even if the first did not provide any relief. Multiple injections are no more likely to provide relief than a single injection, and multiple injections expose patients to additional risks of infection, scarring, and neural injury. If a patient experiences substantial relief from an epidural steroid injection and has a later recurrence of symptoms, consideration may be given for a repeat injection after performing a complete physical exam and ruling out any new pathology.

Surgical treatment should be considered when nonoperative measures have failed or when a profound neurologic deficit such as cauda equina syndrome is present or evolving. Unfortunately, children and adolescents respond less favorably to nonoperative therapy compared with adults, and a significant percentage will require surgical intervention. Although patients with disc herniation may improve with reduction in the local inflammatory response around the nerve root, and also as the disc material loses water volume and shrinks, which eliminates mechanical compression, patients with symptomatic ring apophyseal separations have a bony fragment causing their symptoms and are much less likely to improve spontaneously.

The surgical technique involves removing a small area of the lamina via a posterior approach, called a laminotomy, which allows exposure of the neural elements and underlying disc. Any loose fragments are removed. A bulging disc may also be opened surgically to decompress the area compressing the neural elements, although a complete discectomy is inadvisable. The surgical approach is similar in the case of a slipped vertebral apophysis, in which fragments of bone and cartilage must also be removed. This often requires a bilateral laminotomy to completely address the pathology.

The initial results are excellent in the majority of patients. Up to one-third of patients may have recurrent herniations and resultant symptoms of back or leg pain with longer-term follow-up. These recurrences are initially treated nonoperatively. A spinal fusion may be required when there is instability, for example, a spondylolisthesis.

**Bibliography is available at Expert Consult.**

### 679.9 Tumors

_R. Justin Mistovich and David A. Spiegel_

Back pain may be the most common presenting complaint in children who have a tumor involving the vertebral column or the spinal cord. Other associated symptoms may include weakness of the lower extremities, scoliosis, and loss of sphincter control. The majority of tumors are benign (see Chapter 501), including osteoid osteoma, osteoblastoma, aneurysmal bone cyst, and eosinophilic granuloma. Malignant tumors involving the vertebral column may be osseous, such as osteosarcoma or Ewing sarcoma. The may involve the spinal cord and sympathetic or parasympathetic nerves, in cases of ganglionneuroma, ganglioneuroblastoma, neuroblastoma. Tumors from other primary sites can also metastasize to the spine.

In addition to high-quality plain radiographs, useful imaging modalities include bone scans, which help with localization and identification of other lesions; MRI, which is helpful to identify soft-tissue extension and neurologic compression; and CT, which provides excellent bony detail.

A biopsy is usually required to establish the diagnosis. Treatment of tumors of the spinal column may require a multidisciplinary approach. These cases should ideally be managed in centers with experience in the care patients with these lesions.
Bibliography


Torticollis, literally meaning *twisted neck*, is not a diagnosis but rather a manifestation of a variety of underlying conditions (Table 680-1). Alternative names associated with this condition include *wry-neck* and *cock-robin* deformity.

**CONGENITAL MUSCULAR TORTICOLLIS**

Typically diagnosed during infancy, *congenital muscular torticollis* (CMT) is contracture of the sternocleidomastoid muscle, which results in tilting of the head and neck toward the side of the contracted muscle with rotation to the contralateral side. In the majority of cases (75%)
A muscle-stretching program should be successful in more than 90% of patients with CMT, especially when treatment is started within the first 3 mo of life. Although firm guidelines for imaging the cervical spine have not been established, consideration may be given to obtaining anteroposterior and lateral radiographs of the cervical spine when the typical clinical features associated with CMT are absent or if the deformity does not respond to treatment, as torticollis in infants may be a result of congenital vertebral anomalies. Surgical release of the sternocleidomastoid is considered in patients with persistent deformity despite nonoperative treatment. The muscle may be released at its insertion on the clavicle (unipolar release) or off both its origin and insertion (bipolar release). There is no agreement as to the most appropriate time for the surgical release, but surgical treatment is typically delayed until after 18 mo of age, and some even suggest waiting until the child is approaching school age. Although range of motion can be improved following surgical release even during the teenage years, remodeling of facial asymmetry and plagiocephaly may be less predictable in patients older than infancy. Surgical management results in adequate function and acceptable cosmesis in more than 90% of patients. However with early diagnosis and medical treatment, surgery should only be required in a minority of cases.

OTHER CAUSES OF TORTICOLLIS
The evaluation of torticollis becomes more complex when the typical findings associated with CMT are absent, the usual clinical response is not observed, or when the torticollis presents at a later age. In addition to a careful history and physical examination, consultation with an ophthalmologist and/or neurologist may be helpful. Plain radiographs should be obtained, and an MRI scan of the brain and cervical spine will be required in a subset of cases.

The differential diagnosis is extensive (see Table 680-1). Neurogenic torticollis is uncommon and results from tumors of the posterior fossa or brainstem, syringomyelia (see Chapter 606.3), and Arnold-Chiari malformation (see Chapter 591.11). In addition to the neurologic examination, MRI of the brain and cervical spine is required to establish the diagnosis. Paroxysmal torticollis of infancy is also uncommon and may be a result of vestibular dysfunction. Episodes may last from minutes to days, and the side of the deformity may alternate. The condition is self-limiting, and no specific treatment is required other than ruling out other treatable causes.

Torticollis may also be seen in association with discitis or vertebral osteomyelitis, juvenile idiopathic arthritis, cervical disc calcification, visual problems such as congenital nystagmus or paresis of the superior oblique or lateral rectus muscles, benign or malignant bone tumors, and in patients with cerebral palsy and chronic gastroesophageal reflux (Sandifer syndrome).

Atlantoaxial rotatory displacement represents a spectrum of rotational malalignment from subluxation to frank dislocation between the atlas (C1) and the axis (C2), and may best be described as a pathologic stickiness in the arc of joint motion. In some cases there is fixed malalignment between C1 and C2 (atlantoaxial rotatory fixation) that results in a 50% loss of cervical rotation. The malalignment is often reducible initially but may become irreducible and fixed after weeks to months. As such, prompt diagnosis and treatment are essential. Atlantoaxial rotatory displacement may be diagnosed after infection or inflammation of the tissues of the upper airway, neck, and/or pharynx (Grisel syndrome), following traumatic injuries (usually minor), and as a complication of surgical procedures in the oropharynx, ear, or nose. The diagnosis is established using a dynamic rotational computed tomography scan, in which axial images are obtained through the upper cervical spine with the head rotated maximally toward both the right and the left. If the patient is seen within a few days of the onset of symptoms, then a trial of analgesics and a soft collar may be attempted. Patients with symptoms for more than a week are often admitted to the hospital for analgesia, muscle relaxants, and a period of cervical traction. If this fails to reduce the displacement, then halo traction may be attempted. If the joint can be reduced, patients are typically immobilized for at least 6 wk in a halo vest. Patients with a fixed deformity may require a posterior atlantoaxial fusion to stabilize the right-hand sided sternocleidomastoid muscle is involved, causing the patient’s face and chin to point to the left side.

CMT is thought to be the result of an intratraeune deformation and is more common in first pregnancies and in those with uterine compression syndrome or decreased amniotic fluid volume. CMT may be associated with the presence of a palpable mass (fibrous tissue) within the substance of the sternocleidomastoid muscle in approximately 50% of cases. The mass disappears during infancy and is replaced by a fibrous band. Information from muscle biopsies and magnetic resonance imaging has led to the suggestion that muscle injury from compression and/or stretch may create localized ischemia resulting in fibrosis and subsequent contracture: an intramuscular compartment syndrome. The condition may rarely be caused by hereditary muscle fibrosis and subsequent contracture: an intramuscular compartment syndrome. Associated findings in CMT include plagiocephaly, facial asymmetry, and positional musculoskeletal deformities such as mactarsus adductus (15%) and calcaneovalgus feet. Hip dysplasia may be identified in 8-20% of CMT cases.

Although standards for screening in patients with a normal hip examination have not been established, as many as 15% of patients with CMT have developmental dysplasia of the hip based on screening ultrasound, some of whom required treatment. Consideration should be given to obtaining either an ultrasound scan (4 wks of age) or a plain radiograph of the hips (4-6 mo of age).

Table 680-1 Differential Diagnosis of Torticollis

<table>
<thead>
<tr>
<th>Differential Diagnosis of Torticollis</th>
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<tbody>
<tr>
<td>CONGENITAL</td>
</tr>
<tr>
<td>Muscular torticollis</td>
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<tr>
<td>Positional deformation</td>
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<tr>
<td>Vertebral anomalies (failure segmentation, formation or both)</td>
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<tr>
<td>Unilateral atlantooccipital fusion</td>
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<tr>
<td>Klippel-Feil syndrome</td>
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<tr>
<td>Unilateral absence of sternocleidomastoid</td>
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<tr>
<td>Pterygoid collii</td>
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<tr>
<td>TRAUMA</td>
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<tr>
<td>Muscular injury (cervical muscles)</td>
</tr>
<tr>
<td>Atlantooccipital subluxation</td>
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<tr>
<td>Atlantoaxial subluxation</td>
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<tr>
<td>C2-3 subluxation</td>
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<tr>
<td>Rotary subluxation</td>
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<tr>
<td>Fractures (C1, others)</td>
</tr>
<tr>
<td>INFLAMMATION</td>
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<tr>
<td>Cervical lymphadenitis</td>
</tr>
<tr>
<td>Retropharyngeal abscess</td>
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<tr>
<td>Cervical vertebral osteomyelitis or diskitis</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Grisel syndrome (nontraumatic rotary subluxation of the atlantoaxial joint caused by inflammation)</td>
</tr>
<tr>
<td>Upper lobe pneumonia</td>
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<tr>
<td>NEUROLOGIC</td>
</tr>
<tr>
<td>Visual disturbances (nystagmus, superior oblique or lateral rectus paresis)</td>
</tr>
<tr>
<td>Dystonic ocular sympathetic reactions (phenothiazines, haloperidol, metoclopramide)</td>
</tr>
<tr>
<td>Cervical cord tumor</td>
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<tr>
<td>Posterior fossa brain tumor</td>
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<tr>
<td>Acoustic neuroma</td>
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<tr>
<td>Seringomyelia</td>
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<tr>
<td>Wilson disease</td>
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<tr>
<td>Dystonia musculorum deformans</td>
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<tr>
<td>OTHER</td>
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<tr>
<td>Acute cervical disk calcification</td>
</tr>
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<td>Sandifer syndrome (gastroesophageal reflex, hiatal hernia)</td>
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<td>Benign paroxysmal torticollis</td>
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<tr>
<td>Bone tumors (eosinophilic granuloma, osteoid osteoma)</td>
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<tr>
<td>Soft-tissue tumor</td>
</tr>
<tr>
<td>Psychogenic</td>
</tr>
</tbody>
</table>

PART XXXII
Differential Diagnosis of Torticollis

Plain radiograph of the hips (4-6 mo of age). Patients with developmental dysplasia of the hip based on screening examination have not been established, as many as 15% of patients with CMT have identified in 8-20% of CMT cases. Hip dysplasia may be asymmetry, and positional musculoskeletal deformities such as metatarsus adductus (15%) and calcaneovalgus feet. Hip dysplasia may be a result of congenital vertebral anomalies. Surgical release of the sternocleidomastoid is considered in patients with persistent deformity despite nonoperative treatment. The muscle may be released at its insertion on the clavicle (unipolar release) or off both its origin and insertion (bipolar release). There is no agreement as to the most appropriate time for the surgical release, but surgical treatment is typically delayed until after 18 mo of age, and some even suggest waiting until the child is approaching school age. Although range of motion can be improved following surgical release even during the teenage years, remodeling of facial asymmetry and plagiocephaly may be less predictable in patients older than infancy. Surgical management results in adequate function and acceptable cosmesis in more than 90% of patients. However with early diagnosis and medical treatment, surgery should only be required in a minority of cases.

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The differential diagnosis is extensive (see Table 680-1). Neurogenic torticollis is uncommon and results from tumors of the posterior fossa or brainstem, syringomyelia (see Chapter 606.3), and Arnold-Chiari malformation (see Chapter 591.11). In addition to the neurologic examination, MRI of the brain and cervical spine is required to establish the diagnosis. Paroxysmal torticollis of infancy is also uncommon and may be a result of vestibular dysfunction. Episodes may last from minutes to days, and the side of the deformity may alternate. The condition is self-limiting, and no specific treatment is required other than ruling out other treatable causes.

Torticollis may also be seen in association with discitis or vertebral osteomyelitis, juvenile idiopathic arthritis, cervical disc calcification, visual problems such as congenital nystagmus or paresis of the superior oblique or lateral rectus muscles, benign or malignant bone tumors, and in patients with cerebral palsy and chronic gastroesophageal reflux (Sandifer syndrome).
Traditionally, the classification of KFS has been based on the anatomic distribution of the cervical fusions and the kinematics of the cervical spine in flexion and extension. As more information regarding the genetics of this condition has become available, the classification system has incorporated these changes. KF 1 involves a fusion at C1 with or without a more caudal fusion level (autosomal recessive) and is associated with severe anomalies. KF 2 has a fusion of C2 and C3 with or without a more caudal fusion (autosomal dominant with 100% penetrance). KF 3 is an isolated fusion caudal to C1 and C2/3 (autosomal dominant or recessive). KF 4 (X-linked dominant) is synonymous with Wildervanck syndrome, which involves congenital cervical synostosis associated with hearing loss and the Duane anomaly (congenital rare type of strabismus).

CLINICAL PRESENTATION
KF is present at birth but does not usually become clinically apparent until the 2nd or 3rd decades, when patients present with pain, loss of motion, and/or neurologic symptoms. Given that the same physiologic stresses are applied to a smaller number of mobile spinal segments, patients are at risk for the development of hypermobility and often instability, especially at motion segments adjacent to the fused vertebrae. Weakness or clumsiness may be the presenting symptoms. A complete history is essential, including a detailed family and birth history and review of systems.

PHYSICAL EXAMINATION
A comprehensive musculoskeletal and neurologic examination is required, given associated anomalies in the musculoskeletal and visceral systems. Scoliosis is present in more than 50% of patients with KFS, and congenital anomalies may be identified in other regions of the spine as well. The neurologic exam focuses on identifying any signs of radiculopathy or myelopathy. Spinal cord compression (myelopathy) may result from stenosis or instability, and may result in upper motor neuron signs such as hyperreflexia, Babinski’s sign, and sustained clonus, with more than 3 beats considered pathologic. Nerve root compression (radiculopathy) may be from stenosis and is identified by weakness or decreased sensation in the muscles or dermatomes served by a particular nerve root, respectively.

Figure 680-1 Clinical picture of a 5 yr old with Klippel-Feil syndrome. A, Note short neck and low hairline. B and C, Radiographs of the cervical spine (B, flexion; C, extension) demonstrate congenital fusion and evidence of spinal instability (arrow). (From Drummond DS: Pediatric cervical instability. In Weisel SE, Boden SD, Wisnecki RI, editors: Seminars in spine surgery, Philadelphia, 1996, WB Saunders, pp. 292–309.)
Bibliography
**RADIOGRAPHIC INVESTIGATION**

Initial radiologic evaluation should include an anteroposterior, lateral, and oblique view of the cervical spine. The characteristic finding is a congenital fusion of 2 or more vertebrae (failure of segmentation); however, multiple vertebrae may be involved. Because congenital anomalies may exist in more than 1 region of the spine, radiographs of the thoracic and lumbosacral spine should be routinely obtained. Flexion–extension lateral views of the cervical spine may help to identify segments with excessive motion. Referral to an orthopedist is appropriate if the diagnosis is established. Patients with this condition usually undergo CT and MRI of the spine to accurately characterize the bony anomalies and identify any coexisting neural pathology. A renal ultrasound is routinely obtained, and additional tests may be indicated.

**TREATMENT**

The 3 patterns commonly associated with instability include (1) C2/C3 fusion with occipitocervical synostosis, (2) extensive fusion over multiple levels with an abnormal occipitocervical junction, and (3) 2 fused segments separated by an open joint space. Pain may often be controlled by activity restriction, intermittent immobilization, or other nonoperative modalities. Patients who are chronically symptomatic and/or have instability with positive neurologic symptoms and/or findings, or are felt to be at increased risk for neurologic deterioration, are candidates for surgical treatment. Operative interventions include decompression of a nerve root(s) or the spinal cord, and/or spinal fusion to address spinal instability.

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**Table 680-2 Causes of Pediatric Cervical Instability**

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>SUBTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas)</td>
</tr>
<tr>
<td></td>
<td>Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process)</td>
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<tr>
<td></td>
<td>Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis)</td>
</tr>
<tr>
<td></td>
<td>Syndromic disorders (i.e., Down syndrome, Klippel-Feil syndrome, 22q11.2 deletion syndrome, Larsen syndrome, Marfan syndrome, Ehlers-Danlos syndrome)</td>
</tr>
<tr>
<td>Acquired</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Infection (pyogenic/granulomatous)</td>
</tr>
<tr>
<td></td>
<td>Tumor (including neurofibromatosis)</td>
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<tr>
<td></td>
<td>Inflammatory conditions (i.e., juvenile idiopathic arthritis)</td>
</tr>
<tr>
<td></td>
<td>Osteochondrodysplasias (i.e., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia)</td>
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<tr>
<td></td>
<td>Storage disorders (i.e., mucopolysaccharidoses)</td>
</tr>
<tr>
<td></td>
<td>Metabolic disorders (rickets)</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous (including osteogenesis imperfecta, postsurgery)</td>
</tr>
</tbody>
</table>

**OS ODONTOIDEUM**

Os odontoideum is the most common anomaly of the odontoid peg (dens) and radiographically appears as an oval-shaped, well-corticated, bony ossicle that is positioned cephalad to the body of the axis. There is a discontinuity in the midportion of the dens, and the upper portion of the dens moves with the ring of C1, narrowing the space available for the spinal cord and placing the spinal cord at risk for injury. The body of the dens is mesenchymal in origin and originates from the 1st cervical vertebra, subsequent separation allows it to then fuse with the C2 vertebra. It is formed by 2 separate ossification centers, 1 on either side of the midline, which fuse and are visible at birth. Three etiologies have been proposed: (1) that the os odontoideum represents a fracture nonunion of the odontoid peg; (2) that the os odontoideum represents damage to the epiphyseal plate that has occurred in the 1st yr of life; and (3) that the os odontoideum represents a congenital malformation of the dens itself. The most widely accepted etiology is that a fracture of the dens occurs and subsequently develops a nonunion.

The symptoms and physical findings vary with the location of compression or impingement. In a large series, the average age at presentation was 18.9 yr. The most common presenting symptom was neck pain followed by upper- and lower-limb paresthesia, while torticollis, neck stiffness, gait disturbance, and headaches were uncommon symptoms at presentation. Neurologic examination may reveal a combination of both upper and lower motor neuron signs. Some patients are completely asymptomatic with the anomaly noted incidentally on a lateral cervical spine radiograph.

The radiographic evaluation begins with anteroposterior, lateral, and open mouth (odontoid) views, which may be supplemented by flexion and extension lateral radiographs. CT provides the best bony detail and is useful in defining each anomaly. MRI, including dynamic images in flexion and extension, is best for evaluating neurologic impingement. Symptomatic treatment may be helpful; however, patients with cervical instability and/or neurologic impingement require surgical decompression with or without stabilization.

**DOWN SYNDROME**

Ligamentous hyperlaxity is a characteristic feature of Down syndrome and may result in hypermobility or instability at the occipitoatlantal or the atlantoaxial joints in 10–30% of patients (see Chapter 81). These patients may also have coexisting congenital or developmental...
Bibliography
anomalies of the cervical spine such as occipitalization of the atlas, atlantal arch hypoplasia, basilar invagination, and odontoidem.

Even though the natural history of this spectrum of pathology remains unknown, a subset of patients may develop or be at significant risk of developing neurologic dysfunction. The clinical diagnosis of neurologic dysfunction may be challenging, and subtle findings, such as decreased exercise tolerance and gait abnormalities, including increased tripping or falling, may be the earliest signs of myelopathy. In addition to a neurologic examination, focusing on the presence of long tract signs, imaging studies (plain films, MRI) are required to evaluate patients suspected of having neurologic involvement.

All patients require screening by history and physical examination (at regular intervals) and at least a single series of cervical spinal radiographs, including a lateral view in flexion and extension. Plain radiographs are the preliminary imaging modality used to evaluate for hypermobility or instability. The atlantodens interval (ADI) is used to evaluate the relationship between C1 and C2 (atlantoaxial joint) and is measured as the space between the dens and the anterior ring of C1 (ADI) on lateral radiographs in neutral, flexion, and extension (Fig. 680-2). Although the ADI should be 3 mm or less in the population without Down syndrome, a normal ADI in children with Down syndrome is <4.5 mm. Hypermobility is diagnosed as an ADI between 4.5 and 10 mm, while an ADI >10 mm represents instability and carries a significant risk of neurologic injury. MRI is indicated to detect neurologic involvement in patients with radiographic instability. Recommendations for surveillance of the cervical spine in children with Down syndrome remain varied. Routine clinical evaluations, including a neurologic examination, should be performed; the indications for repeating imaging studies in the absence of clinical symptoms or findings have not been defined. Surveillance helps to define the most appropriate level of physical activity and to identify the small subset of those with either progressive hyperlaxity or instability. Although the specific recommendations vary between states, both clinical and radiographic screenings are also required prior to participation in the Special Olympics. Patients with normal radiographs who are also neurologically normal may be allowed to participate in full activity. Those who are diagnosed with hypermobility may be restricted from contact sports and other high-risk activities that increase the risk of trauma to the cervical spine. Patients with C1-C2 instability with or without neurologic findings are candidates for an atlantoaxial fusion. The risks of a major complication are extremely high for a posterior cervical fusion in this population and include death, neurologic deterioration, and pseudarthrosis with or without graft resorption.

Although hypermobility at the occipitoatlantal joint is present in >50% of children with Down syndrome, most patients do not develop instability or neurologic symptoms. The relationships at this articulation are difficult to measure reliably on plain radiographs and an MRI in flexion and extension is required to evaluate any questionable radiographic findings, especially in the presence of symptoms. Involvement of the subaxial spine is less common and is typically encountered in the adult population of patients with Down syndrome, where degenerative changes and/or instability may result in pain, radiculopathy, and/or myelopathy.

22q11.2 DELETION SYNDROME

The chromosome abnormality deletion of 22q11.2 is a common genetic syndrome, with an overall prevalence of 1 in 5,950 births, and encompasses a wide spectrum of abnormalities. There are characteristic facial features, cleft palate, and cardiac anomalies. Cervical spine anomalies are also common phenotypic features of this syndrome.

At least 1 developmental variation of the occiput or cervical spine is noted in all patients. The occipital variations observed include platybasia (abnormal flattening of the base of the skull) and basilar impression. Variations in anatomy of C1 include dysmorphic shape, an open posterior arch, and occipitalization; axis variations include a dysmorphic dens and "C2 swoosh" (upswept lamina and posterior elements). A range of cervical vertebral fusions is noted in these patients, the most common being at the C2-3 level. Increased segmental motion in the cervical spine is noted in more than half of these patients, and more than a third of patients have increased segmental motion at more than 1 level. With frequent occurrence of upper cervical spine variations in the 22q11.2 deletion syndrome (Fig. 680-3), advanced imaging of the upper cervical spine and regular follow-up of patients to clarify their clinical course is recommended.

Bibliography is available at Expert Consult.
Bibliography
SHOULDER

The shoulder is a ball-and-socket joint. Although similar to the hip, the shoulder has a greater range of motion because of the size of the humeral head relative to the glenoid, as well as to the presence of scapulothoracic motion. The shoulder positions the hand along the surface of a theoretical sphere in space, with its center at the glenohumeral joint.

Brachial Plexus Birth Palsy

(See also Chapter 99.7.)

Injuries to the brachial plexus can occur in the peripartum time, usually as a result of a stretching mechanism. This palsy is often associated with large fetal size and shoulder dystocia. The incidence is 1-3 per 1,000 live births. The injury can range in severity from neurapraxia, to complete rupture of the nerve roots or avulsion of the nerve root from the spinal cord. More often, the upper roots (C5 and C6) of the brachial plexus are affected, rather than a complete brachial plexus palsy itself (C5-T1). Rarely, in isolation, is a lower plexus injury (C8 and T1) observed. The clinical appearance of a C5-C6 brachial plexus birth palsy (Erb-Duchenne palsy) is the waiter’s tip position. The arm is held in a position of shoulder adduction and internal rotation, elbow extension, and wrist flexion.

Treatment

Occupational therapy should be instituted quickly after brachial plexus injury to maintain passive range of motion of the limb and encourage use of the arm. If the biceps muscle does not demonstrate evidence of recovery by 3 mo of age, or shows persistent weakness at 5 mo of age, a more severe nerve injury may be suspected. MRI and electrodiagnostic testing are not consistently reliable for delineation of nerve injury in this setting. Surgical exploration and nerve grafting of the brachial plexus are then indicated.

After complete or incomplete neurologic recovery shoulder dysplasia and dislocation (analogous to developmental dysplasia of the hip) can occur. This occurs as a result of muscle imbalances in the shoulder. In the typical Erb palsy a child may have a persistent internal rotation contracture of the shoulder as a result of the imbalance of the weak abductors and external rotators and stronger adductors and internal rotators. Infants and older children may require arthroscopic or open reduction of shoulder contractures. Older children with residual weakness in shoulder abduction and external rotation can benefit from muscle transfers. Osteotomies are reserved for children with severely deformed glenohumeral joints and functional impairment from persistent shoulder internal rotation contracture (Fig. 681-1).

Sprengel’s Deformity

Sprengel’s deformity, or congenital elevation of the scapula, is a disorder of development that involves a high scapula and limited scapulothoracic motion. The scapula originates in early embryogenesis at a level posterior to the 4th cervical vertebra, but it descends during development to below the 7th cervical vertebra. Failure of this descent, either unilateral or bilateral, is Sprengel’s deformity. The severity of the deformity depends on the location of the scapula and associated anomalies. The scapula in mild cases is simply rotated, with a palpable or visible bump corresponding to the superomedial corner of the scapula in the region of the trapezius muscle. Function is generally good. In moderate cases, the scapula is higher on the neck and connected to the spine with an abnormal omovertebral ligament or even bone. Shoulder motion, particularly abduction, is limited. In severe cases, the scapula is small and positioned on the posterior neck, and the neck may be webbed. The majority of patients have associated anomalies of the musculoskeletal system, especially in the spine, making spinal evaluation important.

Treatment

In mild cases, treatment is generally unnecessary, although a prominent and unsightly superomedial corner of the scapula can be excised. In more severe cases, surgical repositioning of the scapula with rebalancing of parascapular muscles can significantly improve both function and appearance.

ELBOW

The elbow is the most congruent joint in the body. The stability of the elbow is imparted via this bony congruity as well as through the medial and radial collateral ligaments. Where the shoulder positions the hand along the surface of a theoretical sphere, the elbow positions the hand within that sphere. The elbow allows extension and flexion through the ulnoulnumeral articulation and pronation and supination through the radiocapitellar articulation.
Radial Longitudinal Deficiency

Radial longitudinal deficiency of the forearm comprises a spectrum of conditions and diseases that have resulted in hypoplasia or absence of the radius (Table 681-1). This process was formerly referred to as radial club hand, but the name has been changed to radial longitudinal deficiency, which better characterizes the condition. Clinical characteristics consist of a small, shortened limb with the hand and wrist in excessive radial deviation. Partial or complete absence of the radial structures of the forearm and hand are observed (Fig. 681-3).

Radial longitudinal deficiency can range in severity from mild to severe and has been classified into 4 types (Table 681-2). Radial longitudinal deficiency can be associated with other syndromes such as Holt-Oram and Fanconi anemia (see Table 681-1).

Treatment

The goals for the treatment of radial longitudinal deficiency include centralizing the hand and wrist on the forearm, balancing the wrist, and maintaining appropriate thumb and digital motion. Shortly after birth, parents are encouraged to passively stretch the wrist and hand to elongate the contracted radial soft tissues. Serial casting and splinting are ineffective at this time, because of the small size of the arm.

Surgery for correction of the wrist deformity remains controversial. Historically, for children with good elbow motion, centralization of the wrist on the forearm was performed. However recurrence of the deformity was often observed. For this reason some surgeons have elected to abandon this procedure.

When considering a centralization procedure, the preoperative plan begins with careful examination of the patient; considerations in regard to thumb and elbow function must be made before surgery. The surgery typically occurs when the child is 1 yr of age. Correction of the radius (Fig. 681-1).
The diagnosis is made by history and physical examination, as radiographs are typically normal.

**Treatment**

The annular ligament is reduced by rotating the forearm into supination while holding pressure over the radial head. A palpable click or clunk can be felt. The child recovers active supination immediately and usually has immediate relief of discomfort. Immobilization is not required, but recurrent annular ligament subluxations can occur, and the parents should avoid activities that apply traction to the elbows. Parents can learn reduction maneuvers for recurrent episodes to avoid trips to the emergency department or pediatrician’s office. Recurrent subluxation beyond 5 yr of age is rare. Irreducible subluxations tend to resolve spontaneously, with gradual resolution of symptoms over days to weeks; surgery is rarely indicated.

**WRIST**

The wrist is composed of the 2 forearm bones as well as the 8 carpal bones. The wrist allows flexion, extension, and radial and ulnar deviation through the radiocarpal and midcarpal articulations. Pronation and supination occur, at the wrist, through the distal radial ulnar joint. The wrist is a complex joint with numerous ligamentous and soft-tissue attachments. It has complex kinematics that allows for its generous range of motion, but when these kinematics are altered, significant dysfunction can occur.

**Madelung Deformity**

Madelung deformity is a deformity of the wrist that is characterized as radial and palmar angulations of the distal aspect of the radius (Fig. 681-5). Growth arrest of the palmar and ulnar aspect of the distal radial physis is the underlying cause of this deformity. Bony physeal lesions and an abnormal radiolunate ligament (Vicker's ligament) have been implicated. The deformity can be bilateral and affects girls more than boys.

**Treatment**

Treatment of Madelung's deformity is typically observation. Mild deformities can be observed until skeletal maturity. Moderate to severe deformities that either are painful or limit function may be candidates for surgical intervention. Surgical treatment for Madelung's deformity is often motivated by appearance. Patients and their families may be concerned about the palmar angulation of the wrist as well as the resulting prominent distal ulna.

There are a multitude of surgical options for treating Madelung’s deformity. For the skeletally immature patient, resection of the tethering soft tissue (Vicker’s ligament) and physiolysis (fat grafting of any bony lesion seen within the physis) is often the first option. When Madelung’s deformity is encountered in skeletally mature patients, an osteotomy may be considered. Dorsal closing wedge, dome, and ulnar...
Figure 681-3 Spectrum of phenotypes of radial dysplasia. A, Type 1 radius with a hypoplastic thumb. B, Type IV radius with an absent thumb. C, Radiograph of a type IV radius. D and E, Phocomelic radial deficiency. (From Ho C: Disorders of the upper extremity. In Herring JA, editor: Tachdjian’s pediatric orthopaedics, ed 5, Philadelphia, 2014, WB Saunders, Fig. 15-72, p. 391.)

Figure 681-4 The pathology of nursemaid, or pulled, elbow. The annular ligament is partially torn when the arm is pulled. The radial head moves distally, and when traction is discontinued, the ligament is carried into the joint. (From Rang M: Children’s fractures, ed 2, Philadelphia, 1983, JB Lippincott, p. 193.)

Figure 681-5 Radiograph of an adolescent with Madelung’s deformity.
shortening osteotomies may be used alone or in combination to achieve the desired result.

Long-term considerations of Madelung’s deformity concern the incongruity of the distal radial ulnar joint and resulting premature distal radial ulnar joint arthritis.

Ganglion
As a synovial joint, the wrist articulation is lubricated with synovial fluid, which is produced by the synovial lining of the joint and maintained within the joint by the joint capsule. A defect in the capsule can allow fluid to leak from the joint into the soft tissues, resulting in a ganglion. The term cyst is a misnomer, because this extraarticular collection of fluid does not have its own true lining. The defect in the capsule can occur as a traumatic event, although trauma is rarely a feature of the presenting history. The fluid usually exits the joint in the interval between the scaphoid and lunate, resulting in a ganglion located at the dorsoradial aspect of the wrist. Ganglia can occur at other locations, such as the volar aspect of the wrist, or in the palm as a result of leakage of fluid from the flexor tendon sheaths. Pain is not commonly associated with ganglia in children, and when it is, it is unclear whether the cyst is the cause of the pain. The diagnosis is usually evident on physical examination, especially if the lesion transluminates. Extensor tenosynovitis and anomalous muscles can mimic ganglion cysts, but radiography or MRI is not routinely required. Ultrasonography is an effective, noninvasive tool to support the diagnosis and reassure the patient and family.

Treatment
Regarding the treatment of ganglia in children, consider the vowels AEIOU.

Aspiration: Simple aspiration of the fluid has a high recurrence rate and is painful for children given the large-bore needle required to aspirate the gelatinous fluid. However, in older children who would like to decompress the cyst before considering surgery, this may be reasonable.

Excision: Surgical excision, including excision of the stalk connecting the ganglion to its joint of origin, has a high success rate, although the ganglion can recur.

Injection: Aspiration of the cyst and a simultaneous injection of a corticosteroid have been shown to be effective in treating recurrence in children.

Observation: Up to 80% of ganglia in children younger than 10 yr of age resolve spontaneously within 1 yr of being noticed. If the ganglion is painful or bothersome and the child is older than 10 yr of age, treatment may be warranted.

Ultrasound: For children’s parents who are concerned about the mass and want a radiographic study to confirm the diagnosis, ultrasound is a noninvasive test to confirm the diagnosis.

HAND
The hand and fingers allow complex and fine manipulations. An intricate balance among extrinsic flexors, extensors, and intrinsic muscles allow these complex motions to occur. Congenital anomalies of the hand and upper extremity rank just behind cardiac anomalies in incidence, and like cardiac anomalies, if they are not properly identified and remedied, they can have long-term consequences.

Camptodactyly
Camptodactyly is a nontraumatic flexion contracture of the proximal interphalangeal joint that is often progressive. The small and ring fingers are most often affected. Bilateralism is observed two-thirds of the time. The etiology of camptodactyly is varied. Several different hypotheses have been offered as to the cause of this condition. Camptodactyly can be divided into 3 different types (Table 681-3).

Table 681-3 Classification of Camptodactyly

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Congenital, no sex bias, small finger only</td>
</tr>
<tr>
<td>II</td>
<td>Acquired between ages 7 and 11 yr, typically progressive</td>
</tr>
<tr>
<td>III</td>
<td>Severe, significant contracture, bilateral, and associated with other musculoskeletal syndromes</td>
</tr>
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</table>


Treatment
Non-surgical treatment is the primary treatment of camptodactyly. Mild contractures of <30 degrees are usually well tolerated and do not need treatment. Serial casting and static and dynamic splinting are the treatments of choice for preventing progression of contractures. This should be performed until the child is skeletally mature.

Surgical treatment is limited to the treatment of severe contractures. At the time of surgery, all contracted and anomalous structures are released. Results of contracture release for camptodactyly are mixed; often a loss of flexion results from an attempt to improve extension.

Clinodactyly
Angular deformity of the digit in the coronal plane, distal to the metacarpophalangeal joint, is clinodactyly. The most commonly observed finding is a mild radial deviation of the small finger at the level of the distal interphalangeal joint. This is often because of a triangular or trapezoidal middle phalanx. In some cases, a disruption of the physis at the middle phalanx produces a longitudinal epiphysial bracket. This

Figure 681-6 Clinodactyly of the thumb.
bracket is thought to be the underlying cause for the formation the “delta phalanx” that is often observed in clinodactyly. Clinodactyly has been observed in other fingers, including the thumb (Fig. 681-6) and ring finger.

Treatment
Often the treatment for clinodactyly is observation and not surgery. For severe deformities and for those affecting the thumb, surgery may be indicated. Surgery is technically demanding. Bracket resections, corrective osteotomies, and growth plate ablations are the most common procedures performed to correct the observed angular deformities. Results are good and recurrences are few when an appropriate procedure is performed.

Polydactyly
Polydactyly or duplication of a digit can occur either as a preaxial deformity (involving the thumb) or as a postaxial deformity (involving the small finger) (Table 681-4; Fig. 681-7). Each has an inherited and genetic component. Duplication of the thumb occurs more often in whites and Asians and is often unilateral, whereas duplication of the small finger occurs more frequently in African-Americans and may be bilateral. Transmission is typically in an autosomal dominant pattern and has been linked to defects in genes localized to chromosome 2.

Duplication of the thumb is subdivided on the basis of the degree of duplication. Table 681-5 lists the 7 types. Small finger duplication has been further subdivided into 2 types. Type A is a well-formed digit. Type B is a small, often underdeveloped supernumerary digit.

Treatment
Thumb and small finger duplication is typically treated with ablation of the supernumerary digit. Treatment options vary based on the

Table 681-4  Syndromes Associated with Polydactyly

<table>
<thead>
<tr>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Carpenter syndrome</td>
</tr>
<tr>
<td>Ellis-van Creveld syndrome</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
</tr>
<tr>
<td>Polysyndactyly</td>
</tr>
<tr>
<td>Trisomy 13</td>
</tr>
<tr>
<td>Orofaciodigital syndrome</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
</tr>
</tbody>
</table>

Figure 681-7  Several types of central polydactyly are recognized. Type I central polydactyly is characterized by no skeletal attachment of a soft-tissue mass. (No illustration of this unusual type is provided.) A, Type IIA central polydactyly: duplication on a common metacarpal or phalanx without syndactyly. B, Type IIB central polydactyly: duplication on a common metacarpal or phalanx with syndactyly to adjacent digits, which is often manifested as an extra digit hidden within a syndactyly. C, Type III central polydactyly. A complete duplication, including the metacarpal, is a rare anomaly. D, Relationship of central polydactyly and cleft hand. (From From Ho C: Disorders of the upper extremity. In Herring JA, editor: Tachdjian’s pediatric orthopaedics, ed 5, Philadelphia, 2014, WB Saunders, Fig. 15-99, p. 416.)
degree of involvement. Less-well-formed digits can be treated with suture ligation. Well-formed digits require reconstructive procedures that preserve important structures such as the collateral ligaments and nail folds (Fig. 681-8).

**Thumb Hypoplasia**

Hypoplasia of the thumb is a challenging condition for both the patient and the doctor. The thumb represents approximately 40% of hand function. A less-than-optimal thumb can severely limit a patient’s function as the patient grows and develops. Hypoplasia of the thumb can range from being mild with slight shortening and underdeveloped musculature to complete absence of the thumb (Fig. 681-9). Radiographs are useful to help determine osseous abnormalities. The most important finding on physical exam is the presence or absence of a stable carpometacarpal joint. This finding helps guide surgical treatment.

**Treatment**

If the thumb has a stable carpometacarpal joint, reconstruction is advised. Key elements of thumb reconstruction include rebuilding the ulnar collateral ligament of the metacarpophalangeal joint, tendon transfers to aid thumb abduction, and procedures to deepen the web space.

If a stable carpometacarpal joint is not present or the thumb is completely absent, pollicization (surgical construction of a thumb from a finger) is the definitive treatment. Pollicization is a complex procedure rotating the index finger along its neurovascular pedicle to form a thumb. This procedure is typically performed at around 1 yr of age and may be followed by subsequent procedures to deepen the web space or augment abduction (Fig. 681-10).

**Syndactyly**

Failure of the individual digits to separate during development produces syndactyly. Syndactyly is one of the more common anomalies observed in the upper limb (Table 681-6). It is seen in 0.5 of 1,000 live births. Syndactyly can be classified as simple (skin attachments only), complicated (bone and tendon attachments), complete (fusion to the tips, including the nail), or incomplete (simple webbing).

**Treatment**

Division of the conjoined digits should be considered before the 2nd yr of life. Border digits should be divided earlier (3-6 mo) because of concern for tethered growth of digits of unequal length. Digits of similar size, such as the ring and middle, may wait until the child is older to consider separation. Reconstruction of the web space and nail folds as well as appropriate skin-grafting techniques must be used to ensure the best possible functional and cosmetic result (Fig. 681-11).

**Fingertip Injuries**

Young children are fascinated with doorjambs or car doors and other tight spaces, making crush injuries to the fingertips quite common.

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**Table 681-5** Wassel Classification of Thumb Duplication

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CHARACTERISTICS</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Bifid distal phalanx</td>
</tr>
<tr>
<td>II</td>
<td>Duplicate distal phalanx</td>
</tr>
<tr>
<td>III</td>
<td>Bifid proximal phalanx</td>
</tr>
<tr>
<td>IV</td>
<td>Duplicate proximal phalanx</td>
</tr>
<tr>
<td>V</td>
<td>Bifid metacarpal</td>
</tr>
<tr>
<td>VI</td>
<td>Duplicate metacarpal</td>
</tr>
<tr>
<td>VII</td>
<td>Triphalangeal component</td>
</tr>
</tbody>
</table>

Injury can range from a simple subungual hematoma to complete amputation of part or the entire fingertip. Radiographs are important to rule out fractures. Physal fractures associated with nail bed injuries are open fractures with a high risk of osteomyelitis, growth arrest, and deformity if not treated promptly with formal surgical debridement and reduction. Tuft fractures involving the very distal portion of the distal phalanx are common and require little specific treatment other than that for the soft-tissue injury.

The treatment of the soft-tissue injury depends on the type of injury. For suture repairs, only absorbable sutures should be used, because suture removal from a young child's fingertip can require sedation or general anesthesia. If a subungual hematoma exists but the nail is normal and no displaced fracture exists, the nail need not be removed for nail bed repair. If the nail is torn or avulsed, the nail should be removed, the nail bed and skin should be repaired with absorbable sutures, and the nail (or a piece of foil if the nail is absent) should be replaced under the eponychial fold to prevent scar adhesion of the eponychial fold to the nail bed that can prevent nail regrowth.

If the fingertip is completely amputated, treatment depends on the level of amputation and the age of the child. Distal amputations of skin in children younger than 2 yr of age can be replaced as a composite graft with a reasonable chance of surviving. Similar amputations in older children can heal without replacing the skin as long as no bone is exposed and the amputated area is small. A variety of coverage procedures exist for amputations through the mid-portion of the nail. Amputations at or proximal to the proximal edge of the fingernail should be referred emergently to a replant center for consideration for microvascular replantation. When referring, all amputated parts should be saved, wrapped in saline-soaked gauze, placed in a watertight bag, and then placed in ice water. Ice should never directly contact the part, because it can cause severe osmotic and thermal injury.

**Trigger Thumb and Fingers**

The flexor tendons for the thumb and fingers pass through fibrous tunnels made up of a series of pulleys on the volar surface of the digits. These tunnels, for reasons that are not well understood, can become tight at the most proximal or first annular pulley. Swelling of the underlying tendon occurs, and the tendon no longer glides under the pulley. In children, the most common digit involved is the thumb. It has classically been thought to be a congenital problem, but prospective screening studies of large numbers of neonates have failed to find a single case in a newborn child. The incidence of trigger thumb is approximately 3 per 1,000 children at 1 yr of age. Trauma is rarely a feature of the history, and the condition is often painless. Overall function is rarely impaired. A trigger thumb typically manifests with the inability to fully extend the thumb interphalangeal joint. A palpable nodule can be felt in the flexor pollicis longus tendon at the base of the thumb metacarpal phalangeal joint volarly. Other conditions can mimic trigger thumb, including the thumb-in-palm deformity of cerebral palsy. Similar findings in the fingers (index through small) are much less common and may be associated with inflammatory conditions such as juvenile rheumatoid arthritis (Fig. 681-12).

**Treatment**

Trigger thumbs spontaneously resolve in up to 30% of children in whom they are diagnosed before 1 yr of age. Spontaneous resolution beyond that age is not common. Corticosteroid injections are effective in adults but are not effective in children and risk injury to the nearby digital nerves. Surgical release of the first annular pulley is curative and is generally performed between 1 and 3 yr of age. Treatment of trigger fingers other than the thumb in children involves evaluation and treatment of any underlying inflammatory process and in some cases surgical decompression of the flexor sheath and possible flexor tendon partial excision.

Bibliography is available at Expert Consult.
Bibliography
Arthrogryposis multiplex congenita refers to a heterogeneous group of muscular, neurologic, and connective tissue anomalies that present with 2 or more joint contractures at birth as well as muscle weakness. It is associated with abnormal contraction of muscle fibers, causing reduced mobility with a decreased active and passive arc of motion. Arthrogryposis is not a specific diagnosis but a descriptive term with various etiologies and complex clinical features, including multiple congenital contractures of various limb joints. It is associated with 200-300 different disorders encompassing malformations, malfunctions, and neurologic deficiencies.

Approximately 1% of all births show some form of contractures of the joints ranging from unilateral clubfoot to pervasive, crippling contractures due to amyoplasia. Overall incidents of arthrogryposis have been reported to be 1 in 5,000-10,000 live births with equal gender ratios.

Although children with arthrogryposis have many other problems, such as micrognathia, nutrition issues, and sucking issues, here we focus on the orthopedic problems frequently seen in this group of children. In the absence of central nervous system lesions, many children have normal intelligence.

ETIOLOGY
In humans, both the intrinsic and extrinsic causes of arthrogryposis are categorized into 6 groups (Fig. 682-1), including a multitude of disorders (Table 682-1).

Neurologic Abnormalities
As one of the most common causes of arthrogryposis, neurologic abnormalities are present in 70-80% of cases. Patchy damage to the anterior horn cells of the spinal cord can lead to characteristic limb posturing of arthrogryposis. Neurologic disorders, such as spinal muscular atrophy and anterior horn disease, including Werdnig-Hoffmann disease, are associated with arthrogryposis; however, the type of anterior horn cell involvement is usually not from spinal muscular atrophy syndrome (Werdnig-Hoffmann disease). Other, less-common neurologic disorders include neonatal myasthenia and myotonic dystrophy.

Table 682-1 | Associated Etiologies of Arthrogryposis

<table>
<thead>
<tr>
<th>ARTHROGRYPOSIS CAUSED BY NERVOUS SYSTEM DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Focal anterior horn cell deficiency</td>
</tr>
<tr>
<td>• Generalized anterior horn cell deficiency</td>
</tr>
<tr>
<td>• Structural brain disorder/damage</td>
</tr>
<tr>
<td>• Uncertain location</td>
</tr>
<tr>
<td>(Spastic conditions are excluded)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>DISTAL ARTHROGRYPOSIS SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type I dominant distal</td>
</tr>
<tr>
<td>• Type IIa dominant distal (Gordon syndrome)</td>
</tr>
<tr>
<td>• Type IIb distal</td>
</tr>
<tr>
<td>• Digitotalar dysmorphism</td>
</tr>
<tr>
<td>• Trismus pseudocamptodactyly</td>
</tr>
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<td>• Distal distribution, type not specified</td>
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<table>
<thead>
<tr>
<th>PTERYGIUM SYNDROMES</th>
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<tbody>
<tr>
<td>• Multiple pterygium syndrome</td>
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<tr>
<td>• Lethal multiple pterygium syndrome</td>
</tr>
<tr>
<td>• Popliteal pterygium syndrome</td>
</tr>
<tr>
<td>• Ptosis, scoliosis, pterygia</td>
</tr>
<tr>
<td>• Antecubital webbing syndrome (Liebenberg)</td>
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<table>
<thead>
<tr>
<th>MYOPATHIES</th>
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<tbody>
<tr>
<td>• Emery-Dreifuss muscular dystrophy</td>
</tr>
<tr>
<td>• Hypotonia, myopathy, mild contractures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABNORMALITIES OF JOINTS AND CONTIGUOUS TISSUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Congenital contractual arachnodactyly</td>
</tr>
<tr>
<td>• Freeman-Sheldon syndrome</td>
</tr>
<tr>
<td>• Laxity or hypertonicity with intrauterine dislocation and contractures</td>
</tr>
<tr>
<td>• Larsen syndrome</td>
</tr>
<tr>
<td>• Spondyloepimetaphyseal dysplasia with joint laxity</td>
</tr>
<tr>
<td>• Trisomy 18, extended breech position with bilateral hip dislocation</td>
</tr>
<tr>
<td>• Siblings with bifid humeri, hypertelorism, and hip and knee joint dislocations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SKELETAL DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diastrophic dysplasia</td>
</tr>
<tr>
<td>• Paratresmatometric dysplasia</td>
</tr>
<tr>
<td>• Kniest dysplasia</td>
</tr>
<tr>
<td>• Metatropic dysplasia</td>
</tr>
<tr>
<td>• Campomelic dysplasia</td>
</tr>
<tr>
<td>• Schwartz syndrome</td>
</tr>
<tr>
<td>• Fetal alcohol syndrome with synostoses</td>
</tr>
<tr>
<td>• Osteogenesis imperfecta with bowing/contractures</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>INTRAUTERINE/MATERNAL FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fetal alcohol syndrome with contractures</td>
</tr>
<tr>
<td>• Infections</td>
</tr>
<tr>
<td>• Untreated maternal systemic lupus erythematosus</td>
</tr>
<tr>
<td>• Intrauterine fetal constraint</td>
</tr>
<tr>
<td>• Deformity (pressure)</td>
</tr>
<tr>
<td>• Amniotic fluid leakage</td>
</tr>
<tr>
<td>• Multiple pregnancies</td>
</tr>
<tr>
<td>• Intrauterine tumors</td>
</tr>
<tr>
<td>• Disruption (bands)</td>
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</table>

<table>
<thead>
<tr>
<th>MISCELLANEOUS</th>
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</thead>
<tbody>
<tr>
<td>• Pseudotrisomy 18 with contractures</td>
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<tr>
<td>• Roberts pseudothalidomide syndrome</td>
</tr>
<tr>
<td>• Deafness with distal contractures</td>
</tr>
<tr>
<td>• VACTERL association</td>
</tr>
<tr>
<td>• Multiple abnormalities and contractures not otherwise specified</td>
</tr>
<tr>
<td>ARC</td>
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<table>
<thead>
<tr>
<th>SINGLE JOINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Campomelia</td>
</tr>
<tr>
<td>• Symphalangism</td>
</tr>
<tr>
<td>• “Trigger” finger</td>
</tr>
</tbody>
</table>

![Figure 682-1 Etiology of arthrogryposis. (Modified from Hall JG: Arthrogryposis multiplex congenital: Etiology, genetics, classification, diagnostic approach, and general aspects. J Pediatr Orthop B 6:159-166, 1996.)](image-url)
Muscular Abnormalities
These rare abnormalities affect the function and structure of the muscles. Some muscular diseases associated with arthrogryposis are muscular dystrophies, congenital muscular dystrophies (central core, nemaline, centronuclear), intrauterine myositis and mitochondrial diseases.

Limited Intrauterine Spacing
With a less than 0.1% occurrence rate, uterine constraint is rarely the primary cause of arthrogryposis. Maternal uterine anomalies will occasionally increase contractures of fetal limbs with arthrogryposis already existing. Other known causes are lack of amniotic fluid within the uterus and tumors, such as fibroids that can impinge on uterine space, preventing movement.

Connective Tissue Abnormalities
When the tendons, bones, joints, and joint lining develop atypically, decrease in fetal movement causes congenital contractures. Diseases such as diastrophic dysplasia and metatropic dwarfism result from connective tissue not developing properly. These are specific diagnoses resulting in limited joint motion and not true distal arthrogryposis. Other cases show that individuals who lack normal joint movement have distal joint involvement because the connective tissue develops normally but does not attach to the proper location around a joint bone or joint.

Maternal Diseases
Maternal diseases, such as multiple sclerosis, diabetes mellitus, myasthenia gravis, maternal hyperthermia, infection, drugs, and trauma, are associated with an increased incidence of arthrogryposis. In approximately 10% of neonates born to mothers with myasthenia gravis, maternal antibodies enter the fetal circulation through the placenta, causing transient myasthenia gravis; this inhibits fetal acetylcholine receptors, which leads to damaged fetal muscles.

Intrauterine Vascular Compromise
Inadequate vascular supply to the fetus causes fetal hypoxia resulting in anterior horn cell death, which decreases neurologic and myopathic function, resulting in fetal akinesia and secondary joint contractures. Multiple congenital contractures have been reported in individuals after bleeding throughout pregnancy or after a failed attempt at terminating the pregnancy.

CLASSIFICATION
Arthrogryposis multiplex congenita is divided into subgroups with different signs, symptoms, and causes as a practical way to make a differential diagnosis. Disorders involving primarily limbs such as amyoplasia and distal arthrogryposis are the most common subgroups (Table 682-2). Disorders involving limbs and other body parts typically represent a form of multiple pterygium, which is characterized by a web-like membrane that forms across joints affecting a child’s ability to extend and causing fixed flexion. Disorders with limb involvement and abnormal neurologic function are caused by atypical central nervous system, peripheral nervous system, and damaged or absent anterior horn cells.

Amyoplasia, also known as classic arthrogryposis, is a sporadic symmetric disorder that causes fibrotic replacement of the muscles. Symptoms include externally rotated and abducted shoulders, extended elbows, pronated forearms, flexed fingers and wrists, dislocated hips, feet with severe equinovarus contractures, and extended knees. Involved muscles are hypoplastic and fibrotic. Often patients have midfacial hemangioma. Intelligence is usually normal (Figs. 682-2 and 682-3).

Distal arthrogryposis is an autosomal dominant disorder that primarily affects the distal joints of the limbs. Characteristics of the upper limbs are medially overlapping fingers, clenched fists, ulnar deviation of fingers, camptodactyly, and hypoplasia. Lower limbs show talipes equinovarus, calcaneovalgus, vertical talus, or metatarsus varus (Fig. 682-4).

Ten different types of distal arthrogryposis have been categorized based on specific traits they share with each other.

MANAGEMENT OF ORTHOPEDIC PROBLEMS OF ARTHROGRYPOSIS
When a child is born with arthrogryposis, the many stiff or dislocated joints pose issues of timing and best practices of management.

Table 682-2  Current Labels and OMIM Numbers for the Distal Arthrogryposis Syndromes

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>OMIM NUMBER</th>
</tr>
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<tbody>
<tr>
<td>Distal arthrogryposis type 1</td>
<td>108120</td>
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<tr>
<td>Distal arthrogryposis type 2A (Freeman-Sheldon syndrome)</td>
<td>193700</td>
</tr>
<tr>
<td>Distal arthrogryposis type 2B (Sheldon-Hall syndrome)</td>
<td>601680</td>
</tr>
<tr>
<td>Distal arthrogryposis type 3 (Gordon syndrome)</td>
<td>114300</td>
</tr>
<tr>
<td>Distal arthrogryposis type 4 (scoliosis)</td>
<td>609128</td>
</tr>
<tr>
<td>Distal arthrogryposis type 5 (ophthalmoplegia, ptosis)</td>
<td>108145</td>
</tr>
<tr>
<td>Distal arthrogryposis type 6 (sensorineural hearing loss)</td>
<td>108200</td>
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<tr>
<td>Distal arthrogryposis type 7 (trismus-pseudocamptodactyly)</td>
<td>158300</td>
</tr>
<tr>
<td>Distal arthrogryposis type 8 (autosomal dominant multiple pterygium syndrome)</td>
<td>178110</td>
</tr>
<tr>
<td>Distal arthrogryposis type 9 (congenital contractural arachnodactyly)</td>
<td>121050</td>
</tr>
<tr>
<td>Distal arthrogryposis type 10 (congenital planter contractures)</td>
<td>187370</td>
</tr>
</tbody>
</table>


Figure 682-2 Infant with stiff elbows, wrists, fingers, dislocated left hip, valgus stiff knees, and clubfeet.
create the right splints and braces using appropriate thermoplastics, neoprene, Velcro, and other materials can be simple yet effective (Fig. 682-6).

The therapeutic and orthopedic goal for the child with arthrogrypotic limb deformities is to achieve maximal joint motion and to optimize joint position for function. In the lower extremities, the foot needs to be plantigrade. The knees need to have optimal motion for sitting and standing. Hips need to be stabilized especially if the child has walking potential. In the upper extremities, the goals should

Typically a child can have stiff elbows, dislocated hips, dislocated, hyperextended or contracted knees, and clubfeet (Fig. 682-5). The stiffness and deformity need to be aggressively addressed through a combination of modalities. A team of clinicians including therapists for the upper and lower extremities, orthotists, and orthopedic surgeons will be involved.

Initially, passive range-of-motion exercises and judicious splinting directed and assisted by physical and occupational therapy will help to address the various deformities. Splinting and casting can be augmented by a taping program which can be taught to the family so that the taping can be redone frequently to take advantage of improved range of motion. The ingenuity of the therapists and/or orthotist to

Figure 682-3 Infant with stiff elbows, wrists, fingers, dislocated left hip, clubfeet, and micrognathia.

Figure 682-4 Infant with club feet, stiff knees, dislocated hips, stiff fingers, and facial hemangioma.

Figure 682-5 Child with stiff elbows, wrists, knees, and clubfeet.

Figure 682-6 Infant with splints to extend metatarsophalangeal joints, wrists, and knees.
include positioning of 1 arm for feeding and the other for toileting in cases where there is extreme stiffness. Two-handed activities require some symmetry, which can be a challenging goal with extreme contractures and limited muscle strength.

Although scoliosis is common, it usually does not become a problem until adolescence.

**FOOT PROBLEMS**

Clubfoot deformities are the most commonly seen deformities with arthrogryposis (Fig. 682-7). A clubfoot has components of hindfoot equinus, midfoot varus, and forefoot adduction. Feet in arthrogryposis tend to be resistant to improvement but the traditional methods of treatment are nevertheless employed. Casting is begun shortly after birth in a method known as the Ponseti method. Casts are changed weekly until a plateau is reached and heel cord lengthening is needed. Other deformities such as vertical talus are also seen and are addressed in a similar approach although with appropriately differing techniques.

Persistent stiffness often leads to more comprehensive soft tissue releases. This is typically done around age 6-12 mo and is followed by 1 mo of further casting and additional bracing as needed, especially as the foot is growing. When deformities are not corrected in early childhood, additional bony surgery may be needed later. Some of the approaches to this involve bony wedge osteotomies, lateral column lengthening, bone decancellation or takedown. Ilizarov ring or multiaxial monolateral external fixation with or without osteotomies are used in late correction of residual deformities.

Children with significant deformities are often in ankle foot orthoses through much of their lives to avoid deformity recurrence and to augment the sitting base due to weak leg muscles. A plantigrade, pain free, stable foot is the goal of foot management. Foot stiffness is anticipated and unavoidable in arthrogryposis involving the foot.

**KNEE PROBLEMS**

Knee issues, including knee extension or flexion, subluxation, and stiffness, respond well to therapy and splinting. Knee flexion is more common in arthrogryposis. Infrequently it can structurally be complex and associated with skin webbing known as pterygiums. Pterygiums are resistant to nonsurgical intervention and require plastic Z lengthenings. In the case of a flexion contracture, the quadriceps musculature is often deficient and weak. Sometimes the casting and splinting of the knee contractures is insufficient. Hamstring lengthenings with additional posterior knee capular releases are often needed.

In the case of knee hyperextension, the quadriceps are sometimes fibrotic and weak in spite of seeming to overpower the hamstrings. Casting and splinting should begin shortly after birth, which can be done in conjunction with clubfoot casting following the principles of Ponseti. If splinting and therapy fail, lengthening of the quadriceps can be achieved through release of the lateral medial quadriceps, with proximal detachment of the rectus femoris, lengthening of the quadriceps either percutaneously or through a mini open procedure which may minimize scarring.

Long-standing stiffness may lead to joint surface flattening permanently reducing the arc of motion. Repositioning the arc of motion may improve sitting or standing, a choice to be made by the patient, family and physician. Follow up bracing can help to compensate for weak, fibrotic muscles of the legs.

**HIP PROBLEMS**

Teratologic hip dislocations are common within the spectrum of arthrogryposis and usually require open reduction of the hip. Hips in a child with less upper-extremity involvement and more supple hips that are not pathologically stiff may respond to early treatment with a Pavlik harness. Knee hyperextension can often be treated with physical therapy and serial casting. Careful observation of the hip during knee flexion as tightening of the quadriceps and hip flexors can push the hip into posterior dislocation. Once some knee flexion has been achieved, the Pavlik harness can be useful in further flexing the knee and maintaining hip stability in the infant. Most often the hips are stiff and not reducible closed. For these, open reduction with pelvic reconstruction and femoral osteotomy are commonly required, typically at 1 yr of age. There is some controversy about reducing bilateral hip dislocations as a high failure rate can result in asymmetry of the pelvis, pain, leg length inequality, and stiffness. If a child has little ambulation potential, he may do as well retaining the bilateral hip dislocations and positioning the hips for sitting. Management judgment should be made in conjunction with the family guided by a pediatric hip surgeon.

**Ambulation**

As would be expected walking is more difficult for children with arthrogryposis due to the muscle weakness and limited joint motion. Children with arthrogryposis who walk have lower activity levels and take fewer steps than their peers. Not surprisingly muscle fatigue and pain on exertion was noted in a study that included adults with distal arthrogryposis.

**UPPER-EXTREMITY PROBLEMS**

If splinting and a movement exercise program do not result in optimally functional upper extremities, surgical management may improve use of the arms of the child with arthrogryposis. A typical child with arthrogryposis involvement of the upper extremities has internally rotated arms, extended elbows, flexed wrists, and thumb in palm or clasp thumb deformities (see Figs. 682-2 and 682-3).

Treatment is geared toward optimizing use of the arms and hands particularly for critical activities of daily living, such as feeding and toileting. Therapy to improve motion of the joints is started immediately after birth. Pediatric hand therapists are the optimal leaders of the mobility treatment program. Therapy is augmented by use of splints so that less-extensive surgery will be required. The elbow is the critical length adjuster of the arm, allowing the arm to reach out as is necessary for toileting or to approach the mouth for feeding. If necessary, lack of these motions can be compensated by modified silverware and other adaptive equipment, including arm extenders for grabbing.

**Surgery of the Upper Extremity**

Surgical correction of arthrogryposis upper extremity contractures should be started after 1-3 mo and completed by age 12 mo so that the child can optimize his or her motor development. This allows for improved results optimizing the joint growth remodeling plasticity. One-stage procedures yield the best results. Delays in surgery result in more problems of intraarticular adhesions as well as fixed joint incongruity.

**Shoulder**

Because of the rotational capacity of the shoulder derotation osteotomy of the humerus is only occasionally needed. This is usually done in later childhood.
Elbow
A stiff elbow that does not respond to therapy requires surgical intervention starting with soft tissue and capsular release. Capsulotomy of the posterior elbow combined with a V-Y or Z reconstructive lengthening of the triceps allows improved elbow flexion. The triceps may need to be lengthened. Muscle transfer to the forearm can permit active elbow flexion. Each child needs individual assessment as to available flexor source. Most commonly available is the triceps. An elbow with some flexion is extremely important for arm function. Use of the triceps can create elbow flexion overpowering and contracture.

Wrist
Wrist flexion deformity is improved with soft-tissue balancing as well as partial carpectomies. The carpectomies need to be trapezoidal with more removed from the dorsum and the radial side to balance the wrist flexion contracture as well as the tendency for ulnar deviation. Thumb adduction may require an adductor release with an opponensplasty. Tendon transfers such as transfer of the extensor indicis pollicis to the extensor pollicis longus is helpful for improved function of the thumb in clasp thumb deformity.

Finger stiffness and wrist contractures often respond to therapy and bracing without need for surgery.

Scoliosis
Scoliosis is frequent in arthrogrypotic children, although the reported incidence of between 28% and 66% is probably skewed upward in reports as they reflect the experience of scoliosis surgeons. Scoliosis can be congenital or paralytic. The scoliosis is often accompanied by hip contractures associated with hip dislocation and compensatory lumbar lordosis. Curves <30 degrees can be treated initially with bracing in a thoracolumbar spinal orthosis (TLSO brace). After 40 degrees, spinal fusion is warranted.

Surgical Staging
At Children's Hospital of Philadelphia, surgical treatment of the lower limbs usually begins distally and works proximally. The feet are corrected around 6 mo of age, the knees around 8 mo of age, and the hips around 12 mo of age as pelvic osteotomy is often needed to stabilize the hips properly.

The upper extremities are corrected during infancy when the child is seen early. Hand, physical, and occupational therapy are a critical part of the team to optimize function and function prior to and after surgery. Further surgery as a child may be needed to tweak and optimize functional use of the upper and lower extremities.

Bibliography is available at Expert Consult.
Bibliography
Trauma is a leading cause of death and disability in children older than 1 yr of age (see Chapter 5.1). Several factors make fractures of the immature skeleton different from those involving the mature skeleton. The anatomy, biomechanics, and physiology of the pediatric skeletal system are different from those of adults. This results in different fracture patterns (Fig. 683-1), diagnostic challenges, and management techniques specific to children to preserve growth and function.

Epiphyseal lines, rarefaction, dense growth lines, congenital fractures, and pseudofractures appear on radiographs, which could confuse the interpretation of a fracture. Although most fractures in children heal well with indifferent treatment, some fractures terminate disastrously if handled with inexpertise. The differences in the pediatric skeletal system predispose children to injuries different from those of adults. The important differences are the presence of periosseous cartilage, physes, and a thicker, stronger, more osteogenic periosteum that produces new bone, called callus, more rapidly and in greater amounts. The pediatric bone has low density and more porosity. The low density is from lower mineral content and the increased porosity is the result of an increased number of haversian canals and vascular channels. These differences result in a comparatively lower modulus of elasticity and lower bending strength. The bone in children can fail either in tension or in compression; because the fracture lines do not propagate as in adults, there is less chance of comminuted fractures. Hence, pediatric bone can crush, splinter, and break incompletely, as opposed to adult bone which generally breaks like glass and may comminute.

A common teaching is that joint injuries, dislocation, and ligament disruptions are infrequent in children. Although this is generally true, MRI studies show that ligament damage in ankle injuries may not be as unusual as once thought. Damage to a contiguous physis is more likely. Interdigitating mammillary bodies and the perichondrial ring enhance the strength of the physes. Biomechanically, the physes are not as strong as the ligaments or metaphyseal bone. The physis is most resistant to traction and least resistant to torsional forces. The periosseous cartilage is loosely attached to the shaft of bone and adheres densely to the physeal periphery. The periosteum is usually injured in all fractures, but it is less likely to have complete circumferential rupture, because of its loose attachment to the shaft. This intact hinge or sleeve of periosteum lessens the extent of fracture displacement and assists in reduction and maintenance of reduction. The thick periosteum can also act as an impediment to closed reduction, particularly if the fracture has penetrated the periosteum, or in reduction of displaced growth plate.

683.1 Unique Characteristics of Pediatric Fractures
Keith D. Baldwin, Lawrence Wells, and John P. Dormans

FRACTURE REMODELING
Remodeling is the third and final phase in biology of fracture healing, preceded by the inflammatory and reparative phases. This occurs from a combination of appositional bone deposition on the concavity of deformity, resorption on the convexity, and asymmetric physeal growth. Thus, reduction accuracy is somewhat less important than it is in adults (Fig. 683-2). The 3 major factors that have a bearing on the potential for angular correction are skeletal age, distance to the joint, and orientation to the joint axis. The rotational deformity and angular deformity not in the axis of the joint motion are less likely to remodel. Remodeling is best when the fracture occurs close to the physis, the child has more growth remaining, has less deformity to remodel, and is adjacent to a rapidly growing physis (i.e., the proximal humerus). Remodeling typically occurs over the next several months following injury throughout skeletal maturity. Skeletal maturity is reached in girls between 13 and 15 yr of age, and in boys between 14 and 17 yr of age.

OVERGROWTH
Physeal stimulation from the hyperemia associated with fracture healing causes overgrowth. It is usually prominent in long bones such as the femur. The growth acceleration is usually present for 6 mo to 1 yr following the injury. Femoral fractures in children younger than 10 yr of age often overgrow by 1-3 cm. If external fixation or casting is employed, bayonet apposition of bone may be preferred to
Remodeling in children is often extensive, as in this proximal tibial fracture (A) and as seen 1 yr later (B). (From Dormans JP: Pediatric orthopedics: introduction to trauma, Philadelphia, 2005, Mosby, p. 38.)


Compensate for the expected overgrowth. This overgrowth phenomenon will result in equal or near equal limb lengths at the conclusion of fracture remodeling if the fracture shortens less than 2 cm. After 10 yr of age, overgrowth is less of a problem and anatomic alignment is recommended. In physeal injuries, growth stimulation is associated with use of implants or fixation hardware that can cause chronic stimulus for longitudinal growth.

**PROGRESSIVE DEFORMITY**
Injuries to the physes can be complicated by progressive deformities with growth. The most common cause is complete or partial closure of the growth plate. This can be common in fractures of the distal ulna, distal femur, and proximal tibia. An MRI can be helpful to diagnose percent of physeal closure after such an injury. Harris growth arrest lines may be observed in the setting of asymmetric growth and will point toward the area of growth arrest (Fig. 683-3). As a consequence, angular deformity, shortening, or both, can occur. The partial arrest may be peripheral, central, or combined. The magnitude of deformity depends on the physis involved and the amount of growth remaining.

**RAPID HEALING**
Children’s fractures heal more quickly than adults as a result of children's growth potential and thicker, more active periosteum. As
children approach adolescence and maturity, the rate of healing slows and becomes similar to that of an adult.

Bibliography is available at Expert Consult.

683.2 Pediatric Fracture Patterns
Keith D. Baldwin, Lawrence Wells, and John P. Dormans

The different pediatric fracture patterns are the reflection of a child's characteristic skeletal system. The majority of pediatric fractures can be managed by closed methods and heal well.

PLASTIC DEFORMATION
Plastic deformation is unique to children. It is most commonly seen in the ulna and occasionally the fibula. The fracture results from a force that produces microscopic failure on the tensile side of bone and does not propagate to the concave side (Fig. 683-4). The concave side of bone also shows evidence of microscopic failure in compression. The bone is angulated beyond its elastic limit, but the energy is insufficient to produce a fracture. Thus, no fracture line is visible radiographically (Fig. 683-5). The plastic deformation is permanent, and a bend in the ulna of <20 degrees in a 4 yr old child is expected to correct with growth.

BUCKLE OR TORUS FRACTURE
A compression failure of bone usually occurs at the junction of the metaphysis and diaphysis, especially in the distal radius (Fig. 683-6). This injury is referred to as a torus fracture because of its similarity to the raised band around the base of a classic Greek column. They are inherently stable and heal in 3-4 wk with simple immobilization.

GREENSTICK FRACTURE
These fractures occur when the bone is bent, and there is failure on the tensile (convex) side of the bone. The fracture line does not propagate to the concave side of the bone (Fig. 683-7). The concave side shows evidence of microscopic failure with plastic deformation. It is necessary to break the bone on the concave side because the plastic deformation recoils it back to the deformed position.

COMPLETE FRACTURES
Fractures that propagate completely through the bone are called complete fractures. These fractures may be classified as spiral, transverse, or oblique, depending on the direction of the fracture lines. A rotational force usually creates the spiral fractures, and reduction is easy because of the presence of an intact periosteal hinge. Oblique fractures are in the diaphysis at 30 degrees to the axis of the bone and are inherently unstable. The transverse fractures occur following a 3-point bending force and are easily reduced by using the intact periosteum from the concave side.

EPiphyseal FRACTURES
The injuries to the epiphysis involve the growth plate. There is always a potential for deformity to occur, and hence long-term observation is
Bibliography


necessary. The distal radial physis is the most commonly injured physis. Salter and Harris (SH) classified epiphyseal injuries into 5 groups (Table 683-1 and Fig. 683-8). This classification helps to predict the outcome of the injury and offers guidelines in formulating treatment. SH types I and II fractures usually can be managed by closed reduction techniques and do not require perfect alignment, because they tend to remodel with growth. SH type II fractures of the distal femoral epiphysis need anatomic reduction. The SH type III and IV epiphyseal fractures involve the articular surface and require anatomic alignment (<2 mm displacement) to prevent any step off and realign the growth cells of the physis. SH type V fractures are usually not diagnosed initially. They manifest in the future with growth disturbance. Other injuries to the epiphysis are avulsion injuries of the tibial spine and muscle attachments to the pelvis. Osteochondral fractures are also defined as physeal injuries that do not involve the growth plate.

**CHILD ABUSE**

(See also Chapter 40.)

Fractures are the second most common manifestation of child abuse after skin injury (bruises, burns/abrasions). The orthopedic surgeon sees 30-50% of physically abused children. Child abuse should be expected in nonambulatory children with lower-extremity long-bone fractures. No fracture pattern or types are pathognomonic for child abuse; any type of fracture can result from nonaccidental trauma. The fractures that suggest nonaccidental injury include femur fractures in nonambulatory children (younger than age 18 months), distal femoral metaphyseal corner fractures, posterior rib fractures, scapular spinous process fractures, and proximal humeral fractures. Fractures that were unwitnessed or carry a suspicious or changing story also warrant investigation. A full skeletal survey (as opposed to a “babygram”) is essential in every suspected case of child abuse, because it can demonstrate other fractures in different stages of healing. Radiographically, some systemic diseases mimic signs of child abuse, such as osteogenesis imperfecta, osteomyelitis, Caffey disease, and fatigue fractures. Many hospitals have a multidisciplinary team to evaluate and treat patients who are victims of child abuse; these teams are critical to engage early and preferably in the emergency room setting, as difficulty arises managing these emotionally charged issues in a clinic setting. Dedicated teams are most well equipped to identify and manage these issues. It is mandatory to report these cases to social welfare agencies.

*Bibliography is available at Expert Consult.*

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**Figure 683-6** Buckle fracture is a partial failure in compression: anteroposterior (A) and lateral (B) radiographs of the distal radius. *(From Dormans JP: Pediatric orthopedics: introduction to trauma, Philadelphia, 2005, Mosby, p. 37.)

**Figure 683-7** This displaced distal radius fracture has an ulna fracture that is a greenstick (complete failure on the tensile side with microscopic failure on the compression side).

**Table 683-1** Salter-Harris Classification

<table>
<thead>
<tr>
<th>SALTER-HARRIS TYPE</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Separation through the physis, usually through the zones of hypertrophic and degenerating cartilage cell columns</td>
</tr>
<tr>
<td>II</td>
<td>Fracture through a portion of the physis but extending through the metaphyses</td>
</tr>
<tr>
<td>III</td>
<td>Fracture through a portion of the physis extending through the epiphysis and into the joint</td>
</tr>
<tr>
<td>IV</td>
<td>Fracture across the metaphysis, physis, and epiphysis</td>
</tr>
<tr>
<td>V</td>
<td>Crush injury to the physis</td>
</tr>
</tbody>
</table>

**Figure 683-8** Salter-Harris classification of physeal fractures, types I-V.


Bibliography


PHALANGEAL FRACTURES
The different phalangeal fracture patterns in children include physeal, diaphyseal, and tuft fractures. The mechanism of injury is a direct blow to the finger or a finger trapped in a door (see Chapter 681). Crush injuries of the distal phalanx manifest with severe comminution of the underlying bone (tuft fracture), disruption of the nail bed, and significant soft-tissue injury. These injuries are best managed with antibiotics, tetanus prophylaxis, and irrigation. A mallet finger deformity is the inability to extend the distal portion of the digit and is caused by a hyperextension injury. It represents an avulsion fracture of the physis of the distal phalanx. The treatment is splitting the digit in extension for 3-4 wk. The physeal injuries of the proximal and middle phalanx are similarly treated with splint immobilization. Diaphyseal fractures may be oblique, spiral, or transverse in fracture geometry. They are assessed for angular and rotational deformity with the finger in flexion. The patient should be asked to make a fist. All fingers should point toward the scaphoid. If they do not, a malrotation is suspected, even in the presence of x-rays which appear minimally displaced. Any malrotation or angular deformity requires correction for optimal functioning of the hand. These deformities are corrected with closed reduction, and if unstable, they need stabilization.

FOREARM FRACTURES
Fractures of the wrist and forearm are very common fractures in children, accounting for nearly half of all fractures seen in the skeletally immature. The most common mechanism of injury is a fall on the outstretched hand. Eighty percent of forearm fractures involve the distal radius and ulna, 15% involve the middle third, and the rest are rare fractures of the proximal third of the radius or ulnar shaft. The majority of forearm fractures are torus or greenstick fractures. The torus fracture is an impacted fracture, and there is minimal soft-tissue swelling or hemorrhage. They are best treated in a short arm (below the elbow) cast and usually heal within 3-4 wk. Wrist buckle fractures have also been successfully treated with a removable splint. Impacted greenstick fractures of the forearm tend to be intrinsically stable (no cortical disruption) and may be managed with a soft bandage rather than casting.

Diaphyseal fractures can be more difficult to treat because the limits of acceptable reduction are much more stringent than for distal radial fractures. A significant malunion of a forearm diaphyseal fracture can lead to a permanent loss of pronation and supination, leading to functional difficulties. This is particularly true with malrotation of the fragments. Diaphyseal fractures are vulnerable to rotational malalignment due to insertion of the pronator muscle groups and the supinator groups. This malalignment is particularly hard to assess because the deformity is in the axial plane and is evaluated with anteroposterior (AP) and lateral radiographs (Fig. 683-9). The physical examination focuses on soft-tissue injuries and ruling out any neurovascular involvement. The AP and lateral radiographs of the forearm and wrist confirm the diagnosis. Displaced and angulated fractures require manipulative closed reduction under general anesthesia or conscious sedation. They are immobilized in an above-elbow cast for at least 6 wk. Both bone fractures in older children and adolescents (<10 yr of age) must be followed carefully as they are vulnerable to loss of reduction. Loss of reduction and unstable fractures require open reduction and internal fixation. Fixation may be with intramedullary nails or plate fixation, which yield equivalent results.

DISTAL HUMERAL FRACTURES
Fractures around the elbow receive more attention because more aggressive management is needed to achieve a good result. Many injuries are intraarticular, involve the physeal cartilage, and can result in rare malunion or nonunion. As the distal humerus develops from a series of ossification centers, these ossification centers can be mistaken for fractures by inexperienced eyes. Careful radiographic evaluation is an essential part of diagnosing and managing distal humeral injuries. Observation of soft-tissue swelling and tenderness is critical to pick up subtle injuries. Common fractures include separation of the distal humeral epiphysis (transcondylar fracture), supracondylar fractures of the distal humerus, and epiphyseal fractures of the lateral condyle or medial epicondyle. The mechanism of injury is a fall on an outstretched arm. The physical examination includes noting the location and extent of soft-tissue swelling, ruling out any neurovascular injury, specifically anterior interosseous nerve involvement or evidence of compartment syndrome. A transcondylar fracture in neonates should raise suspicion of child abuse. AP and lateral radiographs of the involved extremity are necessary for the diagnosis. If the fracture is not visible, but there is an altered relationship between the humerus and the radius and ulna or the presence of a posterior fat pad sign, a transcondylar fracture or an occult fracture should be suspected. Imaging studies such as oblique radiographs, CT, MRI, and ultrasonography may be required for further confirmation. Displaced supracondylar fractures may be associated with concomitant neurovascular injury (Fig. 683-10) or, rarely, a compartment syndrome. Neurologic injury may also appear in the postoperative period. Careful neurologic examination of the hand before and after are needed to document and treat nerve injury. Preoperative nerve injury requires immediate attention and treatment of the fracture.

In general, distal humeral fractures need good restoration of anatomic alignment. This is necessary to prevent deformity and to allow for normal growth and development. Closed reduction alone, or in
association with percutaneous fixation, is the preferred method. Open
reduction is indicated for fractures that cannot be reduced by closed
methods, fractures with vascular compromise following closed reduc-
tion, open fractures, or interarticular fractures, particularly in older
children. Inadequate reductions can lead to loss of motion, cubitus
varus, cubitus valgus, and rare nonunion or elbow instability. Elbow
stiffness is not as common as in adult fractures, but may occur with
fractures which are severe or intra-articular.

**PROXIMAL HUMERUS FRACTURES**

Fractures of the proximal humerus account for <5% of fractures in
children. They usually result from a fall onto an outstretched arm. The
fracture pattern tends to vary with the age group. Children younger
than 5 yr of age have an SH I injury, those 5-10 yr of age have metaphy-
seal fractures, and children older than 11 yr of age have SH II injury.
Examination includes a thorough neurologic evaluation, especially of
the axillary nerve. The diagnosis is made on AP radiographs of the
shoulder. An axillary view is obtained to rule out any dislocation. Many
children are too uncomfortable to tolerate this view. In this case, a
Velpeau axillary can be obtained while the arm remains in a sling. SH
I injuries do not require reduction because they have excellent remodel-
ing capacity, and simple immobilization in a sling for 2-3 wk is suf-
ficient. The proximal humerus contributes 80% of the growth to the
humerus. The metaphyseal fractures usually do not need reduction
unless the angulation is >50 degrees. A closed reduction with sling
immobilization adequately treats this fracture. SH II fractures with <30
degrees of angulation and <50% displacement are managed in a sling.
Displaced fractures are treated with closed reduction and further sta-
bilization if unstable. Occasionally, open reduction is required because
of button-holing of the fracture spike through the deltoid or interposi-
tion of the tendon of biceps. The majority of longitudinal growth of
the limb comes from the proximal humeral physis. Additionally, the
glenohumeral joint is capable of a large amount of motion. As such
this area is extremely tolerant to deformity. Indications for open reduc-
tion are rare. However, as adolescents approach adulthood, these frac-
tures will remodel less.

**CLAVICULAR FRACTURES**

Neonatal fractures occur as a result of direct trauma during birth, most
often through a narrow pelvis or following shoulder dystocia. They can
be missed initially and can appear with pseudoparalysis. Childhood
fractures are usually the result of a fall on the affected shoulder or direct
trauma to the clavicle. The most common site for fracture is the junc-
tion of the middle and lateral 3rd clavicle. Tenderness over the clavicle
will make the diagnosis. A thorough neurovascular examination is
important to diagnose any associated brachial plexus injury. Biceps
function is important to assess as it is a prognostic indicator for future
function.

An AP radiograph of the clavicle demonstrates the fracture and can
show overlap of the fragments. Physial injuries occur through the
medial or lateral growth plate and are sometimes difficult to differenti-
ate from dislocations of the acromioclavicular or sternoclavicular joint.
Further imaging such as a CT scan may be necessary to further define
the injury. Posterior medial clavicular physial injuries are particularly
problematic due to their proximity to the great vessels and the trachea.
Closed vs open reduction with a cardiac/thoracic team on standby is
necessary. This can be delayed if there is no sign of vascular or respira-
tory compromise.

The treatment of most clavicle fractures consists of an application of
a figure-of-eight clavicle strap or a simple sling. A figure-of-eight strap
will extend the shoulders and minimize the amount of overlap of the
fracture fragments. Evidence exists for adults — that fractures that are
shortened or displaced result in strength loss of the shoulder without
anatomic reduction and fixation. Many centers are extending that indi-
cation to older adolescents, though the data are currently not as strong
as for adults. If a fracture is tenting the skin, or open or resulting in
neurovascular compromise, surgery is indicated. The physeal fractures
are treated with simple sling immobilization without any reduction
attempt. Often, anatomic alignment is not achieved, nor is it necessary.
The fractures heal rapidly usually in 3-6 wk. A palpable mass of callus
is usually visible in thin children. This remodels satisfactorily in
6-12 mo. Complete restoration of shoulder motion and function is
uniformly achieved.

*Bibliography is available at Expert Consult.*

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**683.4 Fractures of Lower Extremity**

*Keith D. Baldwin, Lawrence Wells, and John P. Dormans*

**HIP FRACTURE**

Hip fractures in children account for <1% of all children’s fractures. These
injuries result from high-energy trauma and are often associated
with injury to the chest, head, or abdomen. Treatment of hip fractures
in children entails a complication rate of up to 60%, an overall avascu-
lar necrosis rate of 50%, and a malunion rate of up to 30%. The unique
blood supply to the femoral head accounts for the high rate of avascular
necrosis. Fractures are classified by the Delbet classification as trans-
physyal separations, translateral fractures, cervicotrochanteric frac-
tures, and intertrochanteric fractures. The management principle
includes urgent anatomic reduction (either open or closed), stable
internal fixation (avoiding the physis if possible), and spica casting.
Urgent management has been associated with a lower rate of avascular
necrosis and superior overall outcomes. Capsular decompression also
has been advocated as decreasing overall pressure on the epiphyseal
vessels, and has been demonstrated experimentally. The clinical results
have been mixed.
Bibliography


FEMORAL SHAFT FRACTURES

Fractures of the femur in children are common. All age groups, from early childhood to adolescence, can be affected. The mechanism of injury varies from low-energy twisting type injuries to high-velocity injuries in vehicular accidents. Femur fractures in children younger than age 2 yr should raise the concern for child abuse. A thorough physical examination is necessary to rule out other injuries and assess the neurovascular status. In the case of high-energy trauma, any signs of hemodynamic instability should prompt the examiner to look for other sources of bleeding. AP and lateral radiographs of the femur demonstrate the fracture. An AP radiograph of the pelvis is obtained to rule out any associated pelvic fracture. Treatment of shaft fractures varies with the age group, as described in Table 683-2.

TRIPLANE AND TILLAUX FRACTURES

Triplane and Tillaux fracture patterns occur at the end of the growth period and are based on relative strength of the bone–physis junction and asymmetric closure of the tibial physis. The triplane fractures are so named because the injury has coronal, sagittal, and transverse components (Fig. 683-12). The Tillaux fracture is an avulsion fracture of the anterolateral aspect of the distal tibial epiphysis. Radiographs and further imaging with CT and 3-dimensional reconstructions are necessary to analyze the fracture geometry. The triplane fracture involves the articular surface and hence anatomic reduction is necessary. The reduction is further stabilized with internal fixation. The Tillaux fracture is treated by closed reduction. Open reduction is recommended if a residual intraarticular step-off persists.

METATARSAL FRACTURES

Metatarsal fractures are common in children. They usually result from direct trauma to the dorsum of the foot. High-energy trauma or
multiple fractures of the metatarsal base are associated with significant swelling. A high index for compartment syndrome of the foot must be maintained and compartment pressures must be measured if indicated. Diagnosis is obtained by AP, lateral, and oblique radiographs of the foot. Most metatarsal fractures can be treated by closed methods in a below-knee cast. Weight bearing is allowed as tolerated. Displaced fractures require closed or open reduction with internal fixation. Percutaneous, smooth Kirschner wires generally provide sufficient internal fixation for these injuries. If the compartment pressure is increased, complete release of all compartments in the foot is necessary.

**TOE PHALANGEAL FRACTURES**

Fractures of the lesser toes are common and are usually secondary to direct blows. They commonly occur when the child is barefoot. The toes are swollen, ecchymotic, and tender. There may be a mild deformity. Diagnosis is made radiographically. Bleeding suggests the possibility of an open fracture. The lesser toes usually do not require closed reduction unless significantly displaced. If necessary, reduction can usually be accomplished with longitudinal traction on the toe. Casting is not usually necessary. Buddy taping of the fractured toe to an adjacent stable toe usually provides satisfactory alignment and relief of symptoms. Crutches and heel walking may be beneficial for several days until the soft-tissue swelling and the discomfort decrease.

**Bibliography is available at Expert Consult.**

**683.5 Operative Treatment**

_Sex_ D. Baldwin, Lawrence Wells, and John P. Dormans

Surgery is required for 4-5% of pediatric fractures. The common indications for operative treatment in children and adolescents include displaced physeal fractures, displaced intraarticular fractures, unstable fractures, multiple injuries, open fractures, failure to achieve adequate reduction in older children, failure to maintain an adequate reduction, and certain pathologic fractures.

The aim of operative intervention is to obtain anatomic alignment and relative stability. Rigid fixation is not necessary as it is in adults for early mobilization. The relatively stable construct can be supplemented with external immobilization. SH types III and IV injuries require anatomic alignment, and if they are unstable, internal fixation is used (smooth Kirschner wires, preferably avoiding the course across the growth plate). Multiple closed reductions of an epiphysial fracture are contraindicated because they can cause permanent damage to the germinal cells of the physes.

**SURGICAL TECHNIQUES**

It is important to take great care with soft tissues and skin. The other indications for open reduction and internal fixation are unstable fractures of the spine, ipsilateral fractures of the femur, neurovascular injuries requiring repair, and, occasionally, open fractures of the femur and tibia. Closed reduction and minimally invasive fixation are specifically used for supracondylar fractures of the distal humerus, phalangeal fractures. Failure to obtain anatomic alignment by closed means is an indication for an open reduction. Percutaneous techniques such as intramedullary fixation and minimally invasive plate osteosynthesis are increasingly popular as well.

As children become older and more similar to adults, techniques become more similar to adult techniques. The classic example of this is the femoral shaft fracture. Newborns may be treated with a soft dressing or Pavlik harness; young children may have a spica cast; older children will often be treated with flexible nails. Adolescents will frequently be treated with rigid intramedullary fixation similar to their adult counterparts.

Table 683-3 summarizes the main indications for external fixation.

The advantages of external fixation include rigid immobilization of the fractures, access to open wounds for continued management, and easier patient mobilization for treatment of other injuries and transportation for diagnostic and therapeutic procedures. The majority of complications with external fixation are pin tract infections, chronic osteomyelitis, and refractures after pin removal.

_Bibliography is available at Expert Consult._

**683.6 Complications of Fractures in Children**

_Sex_ D. Baldwin, Lawrence Wells, and John P. Dormans

Complications of fractures in children can be as the result of the injury itself, of treatment, or of late effects of the injury on growth and development of the limb.

The fracture itself may cause growth arrest; this is most common in the proximal tibia, distal femur, and distal ulna. Fractures about the hip may cause avascular necrosis or premature physeal closure. Unacceptable alignment may cause loss of motion or limb malalignment. Fracture healing may cause cosmetically unappealing bumps or curves in the limb. Injuries to the limbs may cause neurovascular compromise or compartment syndrome. Nonunions are rare in children.
Bibliography


Bibliography
Treatment may complicate fractures. Cast immobilization can result in cast ulcers, either from inadequate padding of bony prominences or from patients placing objects in the cast. Casts that are too tight can cause neurovascular compromise. Patients can get cast saw burns from using cast saws that are too dull to remove the cast. Improperly placed casts can promote fracture displacement. Improper follow-up of fractures can result in malunited fractures. Surgical treatment can be complicated by blood loss, neurovascular compromise, iatrogenic physeal damage and hardware complications such as infection or hardware failure.

Late effects of trauma can be from partial or complete closure of the physis. This can lead to limb angular deformity or shortening. Angular deformities can be treated by hemiepiphysiodesis or osteotomy. Reflex sympathetic dystrophy is another poorly understood late effect of trauma but can be debilitating. Physical and occupational therapists are very helpful in managing this condition. Some evidence exists that vitamin C may be useful in the acute setting of high-risk injuries to prevent this complication.
Bone infections in children are relatively common. Early recognition of osteomyelitis in young patients is of critical importance; prompt institution of appropriate medical and surgical therapy before extensive infection develops will minimize permanent damage. The risk is greatest if the physis (the growth plate of bone) is damaged.

**ETIOLOGY**

Bacteria are the most common pathogens in acute skeletal infections. *Staphylococcus aureus* (see Chapter 181.1) is the most common infecting organism in osteomyelitis among all age groups, including newborns. Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) isolates account for more than 50% of *S. aureus* isolates recovered from children with osteomyelitis in some reports. The USA300 clone of *S. aureus* is the most common among CA-MRSA isolates in the United States and is more likely to cause venous thrombosis in children with acute osteomyelitis than other *S. aureus* clones or other bacteria for reasons that are not known.

Group B streptococcus (see Chapter 184) and Gram-negative enteric bacilli (*Escherichia coli*, see Chapter 200) are also prominent pathogens in neonates; group A streptococcus (see Chapter 183) constitutes <10% of all cases. After 6 yr of age, most cases of osteomyelitis are caused by *S. aureus*, streptococcus, or *Pseudomonas aeruginosa* (see Chapter 205). Cases of *Pseudomonas* infection are related almost exclusively to puncture wounds of the foot, with direct inoculation of *P. aeruginosa* from the foam padding of the shoe into bone or cartilage, which develops as osteochondritis. *Salmonella* species (see Chapter 198) and *S. aureus* are the 2 most common causes of osteomyelitis in children with sickle cell anemia (see Chapter 462.1). *Streptococcus pneumoniae* (see Chapter 182) most commonly causes osteomyelitis in children younger than 24 mo of age and in children with sickle cell anemia, but its frequency has declined because of pneumococcal conjugate vaccines. *Bartonella henselae* (see Chapter 209.2) can cause osteomyelitis of any bone, but especially in pelvic and vertebral bones.

*Kingella kingae* (see Chapter 193) may be the second most common cause of osteomyelitis in children younger than 5 yr of age in some parts of the world. The organism is increasingly recognized as a cause of osteomyelitis, spondylodiskitis, and septic arthritis, especially when polymerase chain reaction testing is employed. Nearly 90% of identified *K. kingae* infections have been in young children.

Infection with atypical mycobacteria (see Chapter 217), *S. aureus*, or *Pseudomonas* can occur after penetrating injuries. These organisms as well as coagulase-negative staphylococci or Gram-negative enteric bacteria may cause bone infection related to implanted materials such as spinal instrumentation or any orthopedic hardware. Fungal infections usually occur as a part of multisystem disseminated disease; *Candida* (see Chapter 234) osteomyelitis sometimes complicates fungemia in neonates with or without indwelling vascular catheters.

A microbial etiology is confirmed in approximately 60% of cases of osteomyelitis. Blood cultures are positive in approximately 50% of patients. Prior antibiotic therapy and the inhibitory effect of pus on microbial growth might explain the low bacterial yield.

**EPIDEMIOLOGY**

The median age of children with musculoskeletal infections is approximately 6 yr. Bone infections are more common in boys than girls; the behavior of boys might predispose them to traumatic events. Except for the increased incidence of skeletal infection in patients with sickle cell disease, there is no predilection for osteomyelitis based on race.

The majority of osteomyelitis cases in previously healthy children are hematogenous. Minor closed trauma is a common preceding event in cases of osteomyelitis, occurring in approximately 30% of patients. Infection of bones can also follow penetrating injuries or open fractures. Bone infection following orthopedic surgery is unusually associated with an implanted surgical device. Impaired host defenses also increase the risk of skeletal infection. Table 684-1 lists other risk factors.

**PATHOGENESIS**

The unique anatomy and circulation of the ends of long bones result in the predilection for localization of bloodborne bacteria. In the metaphysis, nutrient arteries branch into nonanastomosing capillaries...
under the physis, which make a sharp loop before entering venous sinusoids draining into the marrow. Blood flow in this area is thought to be “sluggish,” predisposing to bacterial invasion. Once a bacterial focus is established, phagocytes migrate to the site and produce an inflammatory exudate (metaphyseal abscess). The generation of proteolytic enzymes, toxic oxygen radicals, and cytokines results in decreased oxygen tension, decreased pH, osteolysis, and tissue destruction. As the inflammatory exudate progresses, pressure increases spread through the porous metaphyseal space via the haversian system and Volkmann canals into the subperiosteal space. Pusululence beneath the periosteum may lift the periosteal membrane of the bony surface, further impairing blood supply to the cortex and metaphysis.

In newborns and young infants, transphyseal blood vessels connect the metaphysis and epiphysis, so it is common for pus from the metaphysis to enter the joint space. This extension through the physis has the potential to result in abnormal growth and bone or joint deformity. During the latter part of the 1st yr of life, the physis forms, obliterating the transphyseal blood vessels. Joint involvement, once the physis forms, can occur in joints where the metaphysis is intra-articular (hip, ankle, shoulder, and elbow), and subperiosteal pus ruptures into the joint space.

In later childhood, the periosteum becomes more adherent, favoring pus to decompress through the periosteum. Once the growth plate closes in late adolescence, hematogenous osteomyelitis more often begins in the diaphysis and can spread to the entire intramedullary canal. Septic arthritis contiguous with a site of osteomyelitis is also seen in older children with S. aureus osteomyelitis, which may be related to simultaneous hematogenous inoculation of bone and joint space.

**CLINICAL MANIFESTATIONS**

The earliest signs and symptoms of osteomyelitis, often subtle and nonspecific, are generally highly dependent on the age of the patient. Neonates might exhibit pseudoparalysis or pain with movement of the affected extremity (e.g., diaper changes). Half of neonates do not have fever and might not appear ill. Older infants and children are more likely to have pain, fever, and localizing signs such as edema, erythema, and warmth. With involvement of the lower extremities, limp or refusal to walk is seen in approximately half of patients.

Focal tenderness over a long bone can be an important finding. Local swelling and redness with osteomyelitis can mean that the infection has spread out of the metaphysis into the subperiosteal space, representing a secondary soft-tissue inflammatory response. Pelvic osteomyelitis can manifest with subtle findings such as hip, thigh, or abdominal pain. Back pain with or without tenderness to palpation overlying the vertebral processes is noted in vertebral osteomyelitis.

Long bones are principally involved in osteomyelitis (Table 684-2); the femur and tibia are equally affected and together constitute almost half of all cases. The bones of the upper extremities account for 25% of all cases. Flat bones are less commonly affected.

Usually only a single site of bone or joint is involved, although multiple sites of osteomyelitis may be noted in up to 20% of children with S. aureus infections. In neonates, 2 or more bones are involved in almost half of the cases. Children with subacute symptoms and focal findings in the metaphyseal area (usually of tibia) might have a Brodie abscess, with radiographic lucency and surrounding reactive bone. Typically the contents of Brodie abscesses are sterile (Fig. 684-1).

<table>
<thead>
<tr>
<th>BONE</th>
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**Figure 684-1** A, Radiograph demonstrates a lytic lesion in the proximal fibula with laminated thick periostitis. T2-weighted fat-saturated axial (B) and T1-weighted fat-saturated postgadolinium axial (C) magnetic resonance images demonstrate a Brodie abscess with sclerotic outer rim (asterisk) and inner granulation tissue with enhancement (arrowhead). Note the nonenhancing central abscess, which contains a small sequestrum (arrows) that is only seen on the T2-weighted fat-saturated sequence. (From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor: Caffey’s pediatric diagnostic imaging, ed 12, Philadelphia, 2013, WB Saunders, Fig. 138-15, p. 1477.)
Some patients with an adjacent deep venous thrombosis develop septic pulmonary emboli and are more acutely ill than those with a more insidious onset.

**DIAGNOSIS**

The diagnosis of osteomyelitis is clinical; **blood cultures should be performed in all suspected cases**. Depending on the results of imaging studies (see later) aspiration or biopsy of bone or subperiosteal abscess for Gram stain, culture, and possibly bone histology provides the optimal specimen for culture to confirm the diagnosis. These specimens are often obtained by the interventional radiologist or at the time of surgical drainage by the orthopedic surgeon. Direct inoculation of clinical specimens into aerobic blood culture bottles can improve the recovery of *K. kingae*, particularly if held for 1 wk. Polymerase chain reaction appears to be the most sensitive technique to detect *K. kingae*, even up to 6 days after antibiotics are initiated.

There are no specific laboratory tests for osteomyelitis. The white blood cell count and differential, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) are generally elevated in children with bone infections but are nonspecific and not helpful in distinguishing between skeletal infection and other inflammatory processes. The leukocyte count and ESR may be normal during the 1st few days of infection, and normal test results do not preclude the diagnosis of skeletal infection. However, most children with acute hematogenous osteomyelitis have elevations in the ESR and/or CRP. Monitoring elevated ESR and CRP may be of value in assessing response to therapy or identifying complications.

**RADIOGRAPHIC EVALUATION**

Radiographic studies play a crucial role in the evaluation of osteomyelitis. Conventional radiographs, MRI, ultrasonography, CT, and radionuclide studies can all contribute to establishing the diagnosis. Plain radiographs are often used for initial evaluation to exclude other causes such as trauma and foreign bodies. The sequence of radionuclide studies or MRI is often determined by age, site, and clinical presentation.

**Plain Radiographs**

Within 72 hr of onset of symptoms of osteomyelitis, plain radiographs of the involved site using soft-tissue technique and compared to the opposite extremity, if necessary, can show displacement of the deep muscle planes from the adjacent metaphysis caused by deep-tissue edema. Lytic bone changes are not visible on radiographs until 30-50% of the bony matrix is destroyed. Tubular long bones do not show lytic changes for 7-14 days after onset of infection. Infection in flat and irregular bones can take longer to appear.

**Computed Tomography and Magnetic Resonance Imaging**

CT can demonstrate osseous and soft-tissue abnormalities and is ideal for detecting gas in soft tissues. In selected children who cannot remain still or tolerate sedation, CT is a valuable imaging modality. **MRI is more sensitive than CT or radionuclide imaging in acute osteomyelitis** and is the best radiographic imaging technique for identifying abscesses and for differentiating between bone and soft-tissue infection. MRI provides precise anatomic detail of subperiosteal pus and accumulation of purulent debris in the bone marrow and metaphyses for possible surgical intervention. In acute osteomyelitis, purulent debris and edema appear dark, with decreased signal intensity on T1-weighted images, with fat appearing bright (Figs. 684-2 and 684-3). The opposite is seen in T2-weighted images. The signal from fat can be diminished with fat-suppression techniques to enhance visualization. Gadolinium administration can also enhance MRI. Cellulitis and sinus tracts appear as areas of high signal intensity on T2-weighted images. Short tau inversion recovery MRI is a rapid imaging modality for osteomyelitis (Fig. 684-4). MRI can also demonstrate a contiguous or isolated septic arthritis, pyomyositis, or venous thrombosis.

**Radionuclide Studies**

Radionuclide imaging can be valuable in suspected bone infections, especially early in the course of infection and/or if multiple foci are suspected or an unusual site is suspected, as in the pelvis. Technetium-99 methylene diphosphonate (99mTc), which accumulates in areas of increased bone turnover, is the preferred agent for radionuclide bone imaging (3-phase bone scan). Osteomyelitis causes increased vascularity, inflammation, and increased osteoblastic activity, resulting in an increased concentration of 99mTc. Any areas of increased blood flow or inflammation can cause increased uptake of 99mTc in the 1st and 2nd phases, but osteomyelitis causes increased uptake of 99mTc in the 3rd phase (4-6 hr). Three-phase imaging with 99mTc has excellent sensitivity (84-100%) and specificity (70-96%) in hematogenous osteomyelitis and can detect osteomyelitis within 24-48 hr after onset of symptoms. The sensitivity in neonates is much lower, because of poor bone mineralization. Advantages include infrequent need for sedation, lower cost, and the ability to image the entire skeleton for detection of multiple foci.

**DIFFERENTIAL DIAGNOSIS**

Distinguishing osteomyelitis from cellulitis or trauma (accidental or abuse) is the most common clinical circumstance. Myositis or pyomyositis can also appear similar to osteomyelitis with fever, warm and swollen extremities, and limping; tenderness to palpation of the affected soft-tissue area is generally more diffuse than noted in acute osteomyelitis. Nevertheless, distinguishing myositis and pyomyositis from osteomyelitis clinically may be difficult. Myositis and pyomyositis may be isolated but are often found adjacent to an osteomyelitis on MRI. Pyomyositis is most often caused by *S. aureus* followed by group A streptococcus. The pelvic muscles are a common site of pyomyositis...
and can mimic a pelvic osteomyelitis. MRI is the definitive study to identify and localize pelvic pyomyositis (Fig. 684-5). An iliopsoas abscess can manifest with thigh pain, limp, and fever and must be considered in the differential diagnosis of osteomyelitis. The iliopsoas abscess may be primary (hematogenous: *S. aureus*) or secondary to infection in adjacent bone (*S. aureus*), kidney (*E. coli*) or intestine (*E. coli, Bacteroides spp.*). *Mycobacterium tuberculosis* has been reported in patients with HIV infection. Any child with negative bone imaging and a negative hip aspiration, who presents with fever, limp, and elevated inflammatory marks should be evaluated for pyomyositis.

Appendicitis, urinary tract infection, and gynecologic disease are among the conditions in the differential diagnosis of pelvic osteomyelitis. Children with leukemia commonly have bone pain or joint pain as an early symptom. Neuroblastoma with bone involvement may be mistaken for osteomyelitis. Primary bone tumors need to be considered, but fever and other signs of illness are generally absent except in Ewing sarcoma. In patients with sickle cell disease, distinguishing bone infection from infarction may be challenging.

**Chronic recurrent multifocal osteomyelitis (CRMO)** is a nonpyrogenic, sterile inflammatory bone disease that is considered an auto-inflammatory disorder (see Chapter 163). It is also associated with a family history of autoimmune disease; the affected patient may also
have other inflammatory diseases such as Crohn disease, Sweet syndrome, psoriasis, and palmer plantar pustulosis. CRMO in children has many similarities with synovitis, acne, pustulosis, and osteitis seen in adults. In addition, CRMO has similarities to Majeed syndrome, an autosomal recessive disorder with a microcytic dyserythropoietic anemia and with a deficiency of interleukin-1 receptor antagonist, an autosomal recessive autoinflammatory disease.

In contrast to infectious osteomyelitis, CRMO is multifocal, recurrent, and may involve bones not typical of osteomyelitis (spine, pelvis, clavicle, mandible, calcaneus). Plain radiographs reveal osteolytic lesions or sclerosis; whole-body short tau inversion recovery MRI imaging is the diagnostic study of choice (Fig. 684-6), followed by bone scan.

Pain in CRMO is usually insidious, noted at night; fever is not always present. The mean age of onset is 10 yr. The ESR and CRP may be elevated but are not as high as in bacterial osteomyelitis. Pain usually responds to nonsteroidal antiinflammatory drug agents or, in more severe cases, a short course of prednisone.

**TREATMENT**

Optimal treatment of skeletal infections requires collaborative efforts of pediatricians, orthopedic surgeons, and radiologists. Obtaining material for culture (blood, periosteal abscess, bone) before antibiotics are given is essential. Because most patients with osteomyelitis have an indolent, non–life-threatening condition, optimally cultures should be obtained, even if there is a delay of a few hours in initiating antibiotics.

**Antibiotic Therapy**

The initial empirical antibiotic therapy is based on knowledge of likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an antimicrobial agent penicillin, such as nafcillin or oxacillin (150-200 mg/kg/24 hr divided q6h IV), and a broad-spectrum cephalosporin, such as cefotaxime (150-225 mg/kg/24 hr divided q8h IV), provide coverage for the methicillin-susceptible *S. aureus*, group B streptococcus, and Gram-negative bacilli. If methicillin-resistant *Staphylococcus* is suspected, vancomycin is substituted for nafcillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (Gram-negative enteric, *Pseudomonas*, or *S. aureus*) or fungi (*Candida*) should be considered. In older infants and children, the principal pathogens are *S. aureus* and streptococcus.

A major factor influencing the selection of empirical therapy is the rate of methicillin resistance among community *S. aureus* isolates. If methicillin-resistant *S. aureus* (MRSA) accounts for ≥10% of community *S. aureus* isolates, including an antibiotic effective against CA-MRSA in the initial empirical antibiotic regimen is suggested. Vancomycin (60 mg/kg/24 hr divided q6h IV) is the gold standard agent for treating invasive MRSA infections, especially when the child is critically ill. Clindamycin (40 mg/kg/24 hr q8h) is also recommended when the rate of clindamycin resistance is ≤10% among community *S. aureus* isolates, the child is not severely ill and bacteremia is not a concern or blood cultures are known to be negative. Cefazolin (100 mg/kg/24 hr divided q8h IV) or nafcillin (150-200 mg/kg/24 hr divided q6h) is the agent of choice for parenteral treatment of osteomyelitis caused by methicillin-susceptible *S. aureus*. Penicillin is first-line therapy for treating osteomyelitis caused by susceptible strains of *S. pneumoniae* as well as all group A streptococci. Cefotaxime or ceftriaxone is recommended for pneumococcal isolates with resistance to penicillin and for most *Salmonella* spp.

Special situations dictate deviations from the usual empirical antibiotic selection. In patients with sickle cell disease with osteomyelitis, Gram-negative enteric bacteria (*Salmonella*) are common pathogens as well as *S. aureus*, so a broad-spectrum cephalosporin such as cefotaxime (150-225 mg/kg/24 hr divided q8h) is used in addition to vancomycin or clindamycin. Clindamycin (40 mg/kg/24 hr divided q6h IV) is a useful alternative drug for patients allergic to β-lactam drugs. In addition to good antistaphylococcal activity, clindamycin has broad activity against anaerobes and is useful for treating infections secondary to penetrating injuries or compound fractures. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and cefazidime, or with piperacillin–tazobactam and an aminoglycoside. *K. kingae* usually responds to β-lactam antibiotics, including cefotaxime. Although the efficacy of treating osteomyelitis...
caused by *B. henselae* is uncertain, azithromycin plus rifampin may be considered.

When the pathogen is identified and antibiotic susceptibilities are determined, appropriate adjustments in antibiotics are made as necessary. If a pathogen is not identified and a patient’s condition is improving, therapy is continued with the initially selected antibiotic. This selection is more complicated currently owing to the presence of MRSA isolates in the community. If a pathogen is not identified and a patient’s condition is not improving, reaspiration or biopsy and the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and clinical course. For most infections including those caused by *S. aureus*, the minimal duration of antibiotics is 21–28 days, provided that the patient shows prompt resolution of signs and symptoms (within 5–7 days) and the CRP and ESR have normalized; a total of 4–6 wk of therapy may be required. For group A streptococcus, *S. pneumoniae*, or *Haemophilus influenzae* type b, treatment duration may be shorter. A total of 7–10 postoperative days of treatment is adequate for *Pseudomonas* osteochondritis when thorough curettage of infected tissue has been performed. Immunocompromised patients generally require prolonged courses of therapy, as do patients with mycobacterial or fungal infection.

Changing antibiotics from the intravenous route to oral administration when a patient’s condition clearly has improved and the child is afebrile for ≥48–72 hr may be considered. For the oral antibiotic regimen with β-lactam drugs for susceptible staphylococcal or streptococcal infection, cephalaxin (80–100 mg/kg/24 hr q8h) or oral clindamycin (30–40 mg/kg/24 hr q8h) can be used to complete therapy for children with clindamycin-susceptible CA-MRSA or for patients who are seriously allergic or cannot tolerate β-lactam antibiotics. The oral regimen decreases the risk of complications related to prolonged intravenous therapy, is more comfortable for patients, and permits treatment outside the hospital if adherence to treatment can be ensured. Outpatient intravenous antibiotic therapy via a central venous catheter can be used for completing therapy at home, as an alternative; however, catheter-related complications, including infection or mechanical problems, can lead to readmission or emergency department visits.

In children with venous thrombosis complicating osteomyelitis, anticoagulants generally are administered under the supervision of a hematologist until the thrombus has resolved.

**Surgical Therapy**

When frank pus is obtained from subperiosteal or metaphyseal aspiration or is suspected based on MRI findings, a surgical drainage procedure is usually indicated. Surgical intervention is also often indicated after a penetrating injury and when a retained foreign body is possible. In selected cases, catheter drainage performed by an interventional radiologist is adequate.

Treatment of chronic osteomyelitis consists of surgical removal of sinus tracts and sequestrum, if present. Antibiotic therapy is continued for several months or longer until clinical and radiographic findings suggest that healing has occurred. Monitoring the CRP or ESR is not helpful in most cases of chronic osteomyelitis.

**Physical Therapy**

The major role of physical medicine is a preventive one. If a child is allowed to lie in bed with an extremity in flexion, limitation of extension can develop within a few days. The affected extremity should be kept in extension with sandbags, splints, or, if necessary, a temporary cast. Casts are also indicated when there is a potential for pathologic fracture. After 2–3 days, when pain is easing, passive range of motion exercises are started and continued until the child resumes normal activity. In neglected cases with flexion contractures, prolonged physical therapy is required.

**PROGNOSIS**

When pus is drained and appropriate antibiotic therapy is given, the improvement in signs and symptoms is rapid. Failure to improve or worsening by 72 hr requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, or the correctness of the diagnosis. Acute-phase reactants may be useful as monitors. The serum CRP typically normalizes within 7 days after start of treatment, whereas the ESR typically rises for 5–7 days, and then falls slowly, dropping sharply after 10–14 days. Failure of either of these acute-phase reactants to follow the usual course should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Because children are in a dynamic state of growth, sequelae of skeletal infections might not become apparent for months or years; therefore, long-term follow-up is necessary with close attention to range of motion of joints and bone length. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 wk of onset of symptoms provides a better prognosis than delayed treatment.

*Bibliography is available at Expert Consult.*
Chapter 685  •  Septic Arthritis  •  3327

Sheldon L. Kaplan

Without early recognition and prompt institution of appropriate medical and surgical therapy, septic arthritis in infants and children has the potential to damage to the synovium, adjacent cartilage, and bone, and cause permanent disability.

ETIOLOGY

Historically, *Haemophilus influenzae* type b (see Chapter 194) accounted for more than half of all cases of bacterial arthritis in infants and young children. Since the development of the conjugate vaccine, it is now a rare cause; *Staphylococcus aureus* (see Chapter 181.1) is now the most common infection in all age groups. Methicillin-resistant *S. aureus* accounts for a high proportion (>25%) of community *S. aureus* isolates in many areas of the United States and throughout the world. Group A streptococcus (see Chapter 183) and *Streptococcus pneumoniae* (pneumococcus; see Chapter 182) historically cause 10-20%; *S. pneumoniae* is most likely in the 1st 2 yr of life, but its frequency has declined since the introduction of the pneumococcal conjugate vaccines. *Kingella kingae* is recognized as a relatively common etiology with improved culture and polymerase chain reaction methods in children younger than 5 yr old (see Chapters 193 and 684). In sexually active adolescents, gonococcus (see Chapter 192) is a common cause of septic arthritis and tenosynovitis, usually of small joints or as a monoarticular infection of a large joint (knee). *Neisseria meningitidis* (see Chapter 191) can cause either a septic arthritis that occurs in the 1st few days of illness or a reactive arthritis that is typically seen several days after antibiotics have been initiated. Group B streptococcus (see Chapter 184) is an important cause of septic arthritis in neonates.

Fungal infections usually occur as part of multisystem disseminated disease; *Candida* arthritis can complicate systemic infection in neonates with or without indwelling vascular catheters. Primary viral infections of joints are rare, but arthritis accompanies many viral (parvovirus, mumps, rubella live vaccines) syndromes, suggesting an immune-mediated pathogenesis.

A microbial etiology is confirmed in approximately 65% of cases of septic arthritis. Prior antibiotic therapy and the inhibitory effect of synovial fluid on microbial growth might explain the low bacterial yield. Additionally, some cases treated as bacterial arthritis are actually postinfectious (gastrointestinal or genitourinary) reactive arthritis (see Chapter 157) rather than primary infection. Lyme disease produces an arthritis more like a rheumatologic disorder and not typically suppurative.
**Epidemiology**

Septic arthritis is more common in young children. Half of all cases occur by 2 yr of age and three-fourths of all cases occur by 5 yr of age. Adolescents and neonates are at risk of gonococcal septic arthritis.

The majority of infections in otherwise healthy children are of hematogenous origin. Infection of joints can follow penetrating injuries or procedures such as trauma, arthroscopy, prosthetic joint surgery, intraarticular steroid injection, and orthopedic surgery, although this is uncommon. Immunocompromised patients and those with rheumatologic joint disease are also at increased risk of joint infection.

**Pathogenesis**

Septic arthritis primarily occurs as a result of hematogenous seeding of the synovial space. Less often, organisms enter the joint space by direct inoculation or extension from a contiguous focus. The synovial membrane has a rich vascular supply and lacks a basement membrane, providing an ideal environment for hematogenous seeding. The presence of bacterial products (endotoxin or other toxins) within the joint space stimulates cytokine production (tumor necrosis factor-α, interleukin-1) within the joint, triggering an inflammatory cascade. The cytokines stimulate chemotaxis of neutrophils into the joint space, where proteolytic enzymes and elastases are released by neutrophils, damaging the cartilage. Proteolytic enzymes released from the synovial cells and chondrocytes also contribute to destruction of cartilage and synovium. Bacterial hyaluronidase breaks down the hyaluronic acid in the synovial fluid, making the fluid less viscous and diminishing its ability to lubricate and protect the joint cartilage. Damage to the cartilage can occur through increased friction, especially for weight-bearing joints. The increased pressure within the joint space from accumulation of purulent material can compromise the vascular supply and induce pressure necrosis of the cartilage. Synovial and cartilage destruction results from a combination of proteolytic enzymes and mechanical factors.

**Clinical Manifestations**

Most septic arthritides are monoarticular. The signs and symptoms of septic arthritis depend on the age of the patient. Early signs and symptoms may be subtle, particularly in neonates. Septic arthritis in neonates and young infants is often associated with adjacent osteomyelitis caused by transphyseal spread of infection, although osteomyelitis contiguous with an infected joint can be seen at any age (see Chapter 684).

Older infants and children might have fever and pain, with localizing signs such as swelling, erythema, and warmth of the affected joint. With involvement of joints of the pelvis and lower extremities, limp or refusal to walk is often seen.

Erythema and edema of the skin and soft tissue overlying the site of infection are seen earlier in septic arthritis than in osteomyelitis, because the bulging infected synovium is usually more superficial, whereas the metaphysis is located more deeply. Septic arthritis of the hip is an exception because of the deep location of the hip joint.

Joints of the lower extremity constitute 75% of all cases of septic arthritis (Table 685-1). The elbow, wrist, and shoulder joints are involved in approximately 25% of cases, and small joints are uncommonly infected. Suppurative infections of the hip, shoulder, elbow, and ankle in older infants and children may be associated with an adjacent osteomyelitis of the proximal femur, proximal humerus, proximal radius, and distal tibia because the metaphysis extends intraarticularly.

**Diagnosis**

Blood cultures should be performed in all cases of suspected septic arthritis. Aspiration of the joint fluid for Gram stain and culture when the history and physical findings indicate septic arthritis remains the definitive diagnostic technique and provides the optimal specimen for culture to confirm the diagnosis. Most large joint spaces are easy to aspirate, but the hip can pose technical problems; ultrasound guidance facilitates aspiration. Aspiration of joint pus provides the best specimen for bacteriologic culture of infection. If gonococcus is suspected, cervical, anal, and throat cultures should also be obtained. In addition to prompt inoculation onto solid media, inoculation of the specimen in blood culture bottles can increase recovery of *K. kingae*. Polymerase chain reaction appears to be the most sensitive method for detecting *K. kingae* in joint fluid.

Synovial fluid analysis for cell count, differential, protein, and glucose has limited usefulness because noninfectious inflammatory diseases, such as rheumatic fever (see Chapter 183.1) and rheumatoid arthritis (see Chapter 155), can also cause exuberant reaction with increased cells and protein and decreased glucose. Nevertheless, cell counts >50,000-100,000 cells/mm³ generally indicate an infectious process. Synovial fluid characteristics of septic arthritis can suggest infection but are not sufficiently specific to exclude infection. When the joint aspiration is negative, pyomyositis, especially of pelvic muscles, must be excluded by MRI (see Chapter 684).

The white blood cell count and differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are generally elevated in children with joint infections but are nonspecific and might not be helpful in distinguishing between infection and other inflammatory processes. The leukocyte count and ESR may be normal during the first few days of infection, and normal test results do not preclude the diagnosis of septic arthritis. Monitoring elevated ESR and CRP may be of value in assessing response to therapy or identifying complications. In one study of *S. aureus* septic arthritis, risk features for a site of osteomyelitis contiguous with septic arthritis included a CRP >10 mg/dL at the time of admission, positive blood cultures or more than 2 days of fever following admission.

**Radiographic Evaluation**

Radiographic studies play a crucial role in evaluating septic arthritis. Conventional radiographs, ultrasonography, CT, MRI, and radionuclide studies can all contribute to establishing the diagnosis (Fig. 685-1).

**Plain Radiographs**

Plain films of septic arthritis can show widening of the joint capsule, soft-tissue edema, and obliteration of normal fat lines. Plain films of the hip can show medial displacement of the obturator muscle into the pelvis (the obturator sign), lateral displacement or obliteration of the gluteal fat lines, and elevation of Shenton’s line with a widened arc.

**Ultrasonography**

Ultrasonography is particularly helpful in detecting joint effusion and fluid collection in the soft-tissue and subperiosteal regions. Ultrasonography is highly sensitive in detecting joint effusion, particularly for the hip joint, where plain radiographs are normal in more than 50% of cases of septic arthritis of the hip. Ultrasonography can serve as an aid in performing hip aspiration.

### Table 685-1: Anatomic Distribution of Septic Arthritis

<table>
<thead>
<tr>
<th>BONE</th>
<th>PERCENT (%)</th>
<th>BONE</th>
<th>PERCENT (%)</th>
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<tbody>
<tr>
<td>Knee</td>
<td>&gt;40</td>
<td>Interphalangeal</td>
<td>&lt;1</td>
</tr>
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<td>Hip</td>
<td>22-40</td>
<td>Metatarsal</td>
<td>&lt;1</td>
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<td>Ankle</td>
<td>4-13</td>
<td>Sacroiliac</td>
<td>&lt;1</td>
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<td>Elbow</td>
<td>8-12</td>
<td>Acromioclavicular</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Wrist</td>
<td>1-4</td>
<td>Metacarpal</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Shoulder</td>
<td>~3</td>
<td>Toe</td>
<td>~1</td>
</tr>
</tbody>
</table>

Magnetic Resonance Imaging and Computed Tomography

MRI and CT may be useful in confirming the presence of joint fluid in patients with suspected osteoarthritis infections. MRI may be useful in excluding adjacent osteomyelitis.

Radionuclide Imaging

Radionuclide imaging compared to radiographs is more sensitive in providing supportive evidence of the diagnosis of septic arthritis; a scan may be positive within 2 days of the onset of symptoms. Three-phase imaging with technetium-99m methylene diphosphonate shows symmetric uptake on both sides of the joint, limited to the bony structures adjacent to the joint. Radionuclide imaging is also useful for evaluating the sacroiliac joint.

Differential Diagnosis

The differential diagnosis of septic arthritis depends on the joint or joints involved and the age of the patient. For the hip, toxic synovitis, pyomyositis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, psoas abscess, and proximal femoral, pelvic, or vertebral osteomyelitis as well as diskitis should be considered. For the knee, distal femoral or proximal tibial osteomyelitis, pauciarticular rheumatoid arthritis, and referred pain from the hip should be considered. Knee or thigh pain may be referred from the hip. Other conditions such as trauma, cellulitis, pyomyositis, sickle cell disease, hemophilia, and Henoch-Schönlein purpura can mimic purulent arthritis. When several joints are involved, serum sickness, collagen vascular disease, rheumatic fever, and Henoch-Schönlein purpura should be considered. Arthritis is one of the extraintestinal manifestations of inflammatory bowel disease. Reactive arthritis following a variety of bacterial (gastrointestinal or genital) and parasitic infections, streptococcal pharyngitis, or viral hepatitis can resemble acute septic arthritis (see Chapter 157).

TREATMENT

Optimal treatment of septic arthritis requires cooperation of pediatricians, orthopedic surgeons, and radiologists to benefit the patient.

Antibiotic Therapy

The initial empirical antibiotic therapy is based on knowledge of likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an anti-staphylococcal penicillin, such as nafcillin or oxacillin (150-200 mg/kg/24 hr divided q6h IV), and a broad-spectrum cephalosporin, such as cefotaxime (150-225 mg/kg/24 hr divided q6h IV), provide coverage for the S. aureus, group B streptococcus, and Gram-negative bacilli. If methicillin-resistant S. aureus (MRSA) is a concern, vancomycin is selected in stead of nafcillin or oxacillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (S. aureus, Gram-negative enterics, or Pseudomonas aeruginosa) or fungi (Candida) should be considered.

In older infants and children with septic arthritis, empirical therapy to cover for S. aureus, streptococci, and K. kingae includes cefazolin (100-150 mg/kg/24 hr divided q8h) or nafcillin (150-200 mg/kg/24 hr divided q6h).

In areas where methicillin resistance is noted in ≥10% of community-acquired methicillin-resistant S. aureus strains (CA-MRSA), including an antibiotic that is effective against CA-MRSA isolates is suggested. Clindamycin (40 mg/kg divided q8h) and vancomycin (15 mg/kg q6 IV) are alternatives when treating CA-MRSA infections. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime or with extended-spectrum penicillins and β-lactamase inhibitors with an aminoglycoside. Adjunct therapy with dexamethasone for 4 days with antibiotic therapy appeared to benefit children with septic arthritis in one study but has not been studied in children with CA-MRSA septic arthritis.

When the pathogen is identified, appropriate changes in antibiotics are made, if necessary. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the antibiotic selected initially. If a pathogen is not identified and a patient's condition is not improving, reaspiration or the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and the clinical course. Ten to 14 days is usually adequate for streptococci, S. pneumoniae, and K. kingae; longer therapy may be needed for S. aureus and Gram-negative infections. Normalization of ESR and CRP in addition to a normal examination supports discontinuing antibiotic therapy. In selected patients, obtaining a plain radiograph of the joint before completing therapy can provide evidence (typically periosteal new bone) of a previously unappreciated contiguous site of osteomyelitis that would likely prolong antibiotic treatment. Oral antibiotics can be used to complete therapy once the patient is afibrile for 48-72 hr and is clearly improving.

Surgical Therapy

Infection of the hip is generally considered a surgical emergency because of the vulnerability of the blood supply to the head of the femur. For joints other than the hip, daily aspirations of synovial fluid may be required. Generally, 1 or 2 subsequent aspirations suffice. If fluid continues to accumulate after 4-5 days, arthroscopy or video-assisted arthroscopy is needed. At the time of surgery, the joint is flushed with sterile saline solution. Antibiotics are not instilled because they are irritating to synovial tissue, and adequate amounts of antibiotic are achieved in joint fluid with systemic administration.

PROGNOSIS

When pus is drained and appropriate antibiotic therapy is given, the improvement in signs and symptoms is rapid. Failure to improve or worsening by 72 hr requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, and the correctness of the diagnosis. Acute-phase reactants may be useful as monitors. Failure of either of these acute-phase reactants to follow the usual course should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Figure 685-1 MRI of staphylococcal septic arthritis of left hip, with fluid collections between planes of gluteal muscles. Arrows indicate fluid collection. (From Matthews CJ, Weston VC, Jones A, et al: Bacterial septic arthritis in adults, Lancet 375:846–854, 2010.)
Because children are in a dynamic state of growth, sequelae of skeletal infections might not become apparent for months or years; therefore, long-term follow-up is necessary, with close attention to range of motion of joints and bone length. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 wk of onset of symptoms provides a better prognosis than delayed treatment.

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Bibliography


The Centers for Disease Control and Prevention recommend moderate to vigorous physical activity on a regular basis for all adolescents. Physical activity has favorable effects on hypertension, obesity, and serum lipid levels in youth and is associated with lower rates of cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and colon and breast cancer among adults.

Pediatricians should promote physical activity to their patients, especially those with lower rates of physical activity and sports participation, including children with special healthcare needs (see Chapter 717) and those from lower socioeconomic groups. Physicians also have the responsibility of providing medical clearance for participation in physical activity and sports and for diagnosis and rehabilitation of injuries.

Approximately 30 million children and adolescents participate in organized sports in the United States. Approximately 3 million injuries occur annually if injury is defined as time lost from the sport. Deaths in sports are rare, with the majority of nontraumatic deaths caused by cardiac diseases (see Chapter 436). Nonetheless, approximately 30% of life-threatening injuries in children presenting to an emergency room are sports related. Overall, injury rates and injury severity in sports increase with age and pubertal development, related to the greater speed, strength, and intensity of competition.

Identifying mechanisms of injury and establishing and enforcing rules that reduce the likelihood of that mechanism of injury, including penalizing dangerous play, have reduced catastrophic injury rates. Injury rates also have been reduced by removing environmental hazards, such as trampolines in gymnastics and stationary (vs break-away) bases in softball, and by modifying heat injury rates in soccer tournaments by adding water breaks and reducing the playing time. Wearing equipment such as mouth guards can reduce dental injuries. A common reason for re-injury is lack of rehabilitation of old injuries; appropriate rehabilitation reduces injury rates. Preseason training for high school athletes, with an emphasis on speed, agility, jump training, and flexibility, is associated with lower injury rates in soccer and fewer serious knee injuries in female athletes. Traditional stretching maneuvers or massage have not been demonstrated to reduce the risk of injury or muscle soreness, but ankle taping is helpful particularly to prevent re-injury of the ankle. One setting for implementing some of these prevention strategies and for detecting un-rehabilitated injuries and medical problems that could affect participation in sports is the preparticipation sports examination.

PREPARTICIPATION SPORTS EXAMINATION

The preparticipation sports examination (PSE) is performed with a directed history and a directed physical examination, including a screening musculoskeletal examination. It identifies possible problems in 1-8% of athletes and excludes fewer than 1% from participation. The PSE is not a substitute for the recommended comprehensive annual evaluation, which looks at behaviors that are potentially harmful to teens, such as sexual activity, drug use, and violence, and assesses for depression and suicidal ideation and addresses broader issues of prevention. Table 686-1 identifies the purposes of the PSE. If possible, the PSE should be combined with the comprehensive annual health visit with emphasis on preventive healthcare (see Chapters 5 and 16).

State requirements for how often a youth needs a PSE differ, ranging from annually to entry to a new school level (middle school, high school, college). At a minimum, a focused, annual interim evaluation should be done on an otherwise healthy young athlete. The PSE is optimally performed 3-6 wk before the start of practice.

History and Physical Examination

The essential components of the PSE are the history and focused medical and musculoskeletal screening examinations. Identified problems require more investigation (Tables 686-2 and 686-3). In the absence of symptoms, no screening laboratory tests are required.

Seventy-five percent of significant findings are identified by the history; a standardized questionnaire given to the parent and athlete is important because the young athlete might not know or might forget important aspects of his or her history. The questionnaire should include questions about previous medical, surgical, cardiac, pulmonary, neurologic, dermatologic, visual, psychologic, musculoskeletal, and menstrual problems, as well as about heat illness, medications, allergies, immunizations, and diet. The most commonly identified problems are unrehabilitated injuries. An investigation of previous injuries, including diagnostic tests, treatment, and present functional status, is indicated.

Sudden death during sports can result from undetected cardiac disease such as hypertrophic or other cardiomyopathies (see Chapter 439), anomalous coronary vessels (see Chapter 432.2), or a ruptured aorta in Marfan syndrome (see Chapter 702). In many cases, the underlying heart disease is not suspected, and death is the first sign of heart disease (see Chapter 436). However, in approximately 25-50% of cases,
Table 686-3 Medical Conditions and Sports Participation

<table>
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<th>CONDITION</th>
<th>MAY PARTICIPATE</th>
<th>EXPLANATION</th>
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<td>Atlantoaxial instability</td>
<td>Qualified yes</td>
<td>Athlete (particularly if the athlete has Down syndrome or juvenile rheumatoid arthritis with cervical involvement) needs evaluation to assess the risk of spinal cord injury during sports participation, especially when using a trampoline</td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td>Qualified yes</td>
<td>Athlete needs evaluation</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>All sports can be played with proper attention and appropriate adjustments to diet (particularly carbohydrate intake), blood glucose concentrations, hydration, and insulin therapy. Blood glucose concentrations should be monitored before exercise, every 30 min during continuous exercise, 15 min after completion of exercise, and at bedtime</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>Qualified yes</td>
<td>Athlete with an eating disorder needs medical and psychiatric assessment before participation</td>
</tr>
<tr>
<td>Fever</td>
<td>No</td>
<td>Elevated core temperature can indicate a pathologic medical condition (infection or disease) that is often manifest by increased resting metabolism and heart rate. Accordingly, during the athlete’s usual exercise regimen, fever can result in greater heat storage, decreased heat tolerance, increased risk of heat illness, increased cardiopulmonary effort, reduced maximal exercise capacity, and increased risk of hypotension because of altered vascular tone and dehydration. On rare occasions, fever accompanies myocarditis or other conditions that can make usual exercise dangerous</td>
</tr>
<tr>
<td>Heat illness, history of</td>
<td>Qualified yes</td>
<td>Because of the likelihood of recurrence, the athlete needs individual assessment to determine the presence of predisposing conditions and behavior and to develop a prevention strategy that includes sufficient acclimatization (to the environment and to exercise intensity and duration), conditioning, hydration, and salt intake, as well as other effective measures to improve heat tolerance and to reduce heat injury risk (e.g., protective equipment and uniform configurations)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Yes</td>
<td>Because of the apparent minimal risk to others, all sports may be played as athlete’s state of health allows (especially if viral load is undetectable or very low). For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood. Certain sports (such as wrestling and boxing) can create a situation that favors viral transmission (likely bleeding plus skin breaks); if viral load is detectable, then athletes should be advised to avoid such high-contact sports</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment</td>
</tr>
</tbody>
</table>
## Table 686-3  Medical Conditions and Sports Participation—cont’d

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>MAY PARTICIPATE</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathies</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
<td>Because of the increased risk of heat illness and cardiovascular strain, obese athletes particularly need careful acclimatization (to the environment and to exercise intensity and duration), sufficient hydration, and potential activity and recovery modifications during competition and training.</td>
</tr>
<tr>
<td>Organ transplant recipient (and those taking immunosuppressive medications)</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment for contact, collision, and limited-contact sports In addition to potential risk of infections, some medications (e.g., prednisone) increase tendency for bruising</td>
</tr>
<tr>
<td>Skin infections, including herpes simplex, molluscum contagiosum, verrucae (warts), staphylococcal and streptococcal infections (furuncles [boils], carbuncles, impetigo, methicillin-resistant <em>Staphylococcus aureus</em> [cellulitis and/or abscesses]), scabies, and tinea</td>
<td>Qualified yes</td>
<td>During contagious periods, participation in gymnastics or cheerleading with mats, martial arts, wrestling, or other collision, contact, or limited-contact sports is not allowed</td>
</tr>
<tr>
<td>Spleen, enlarged</td>
<td>Qualified yes</td>
<td>If the spleen is acutely enlarged, then participation should be avoided because of risk of rupture If the spleen is chronically enlarged, then individual assessment is needed before collision, contact, or limited-contact sports are played</td>
</tr>
</tbody>
</table>

### CARDIOVASCULAR

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAY PARTICIPATE</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis (inflammation of the heart)</td>
<td>No</td>
<td>Carditis can result in sudden death with exertion</td>
</tr>
<tr>
<td>Hypertension (high blood pressure)</td>
<td>Qualified yes</td>
<td>Those with hypertension &gt;5 mm Hg above the 99th percentile for age, sex, and height should avoid heavy weightlifting and power lifting, bodybuilding, and high-static component sports Those with sustained hypertension (&gt;95th percentile for age, sex, and height) need evaluation The National High Blood Pressure Education Program Working Group report defined prehypertension and stage 1 and stage 2 hypertension in children and adolescents younger than 18 yr of age</td>
</tr>
<tr>
<td>Congenital heart disease (structural heart defects present at birth)</td>
<td>Qualified yes</td>
<td>Consultation with a cardiologist is recommended Those who have mild forms may participate fully in most cases; those who have moderate or severe forms or who have undergone surgery need evaluation The 36th Bethesda Conference defined mild, moderate, and severe disease for common cardiac lesions</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>Qualified yes</td>
<td>If the murmur is innocent (does not indicate heart disease), full participation is permitted; otherwise, athlete needs evaluation (see structural heart disease, especially hypertrophic cardiomyopathy and mitral valve prolapse)</td>
</tr>
</tbody>
</table>

### Dysrhythmia (Irregular Heart Rhythm)

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAY PARTICIPATE</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-QT syndrome</td>
<td>Qualified yes</td>
<td>Consultation with a cardiologist is advised. Those with symptoms (chest pain, syncope, near-syncope, dizziness, shortness of breath, or other symptoms of possible dysrhythmia) or evidence of mitral regurgitation on physical examination need evaluation; all others may participate fully</td>
</tr>
<tr>
<td>Malignant ventricular arrhythmias</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Symptomatic Wolff-Parkinson-White syndrome</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Advanced heart block</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Family history of sudden death or previous sudden cardiac event</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Implantation of a cardioverter-defibrillator</td>
<td>Qualified yes</td>
<td></td>
</tr>
</tbody>
</table>

### Structural or Acquired Heart Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAY PARTICIPATE</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Qualified no</td>
<td>Consultation with a cardiologist is recommended. The 36th Bethesda Conference provided detailed recommendations. Most of these conditions carry a significant risk of sudden cardiac death associated with intense physical exercise. Hypertrophic cardiomyopathy requires thorough and repeated evaluations, because disease can change manifestations during later adolescence. Marfan syndrome with an aortic aneurysm also can cause sudden death during intense physical exercise. An athlete who has ever received chemotherapy with anthracyclines may be at increased risk for cardiac problems owing to the cardiotoxic effects of the medications, and resistance training in this population should be approached with caution; strength training that avoids isometric contractions may be permitted. Athlete needs evaluation</td>
</tr>
<tr>
<td>Coronary artery anomalies</td>
<td>Qualified no</td>
<td></td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Qualified no</td>
<td></td>
</tr>
<tr>
<td>Acute rheumatic fever with carditis</td>
<td>Qualified no</td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome, vascular form</td>
<td>Qualified no</td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Anthracycline use</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Vasculitis, vascular disease</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Kawasaki disease (coronary artery vasculitis)</td>
<td>Qualified yes</td>
<td>Consultation with a cardiologist is recommended. Athlete needs individual evaluation to assess risk on the basis of disease activity, pathologic changes, and medical regimen</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Qualified yes</td>
<td></td>
</tr>
</tbody>
</table>
### Table 686-3  Medical Conditions and Sports Participation—cont’d

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>MAY PARTICIPATE</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EYES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functionally 1-eyed athlete</td>
<td>Qualified yes</td>
<td>A functionally 1-eyed athlete is defined as having best-corrected visual acuity worse than 20/40 in the poorer-seeing eye. Such an athlete would suffer significant disability if the better eye were seriously injured, as would an athlete with loss of an eye. Specifically, boxing and full-contact martial arts are not recommended for functionally 1-eyed athletes, because eye protection is impractical and/or not permitted. Some athletes who previously underwent intraocular eye surgery or had a serious eye injury may have increased risk of injury because of weakened eye tissue. Availability of eye guards approved by the American Society for Testing and Materials and other protective equipment might allow participation in most sports, but this must be judged on an individual basis.</td>
</tr>
<tr>
<td>Loss of an eye</td>
<td>Qualified yes</td>
<td>Athlete with active infectious conjunctivitis should be excluded from swimming</td>
</tr>
<tr>
<td>Detached retina or family history of retinal detachment at young age</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>High myopia</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disorder, such as Marfan or Stickler syndrome</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Previous intraocular eye surgery or serious eye injury</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis, infectious</td>
<td>Qualified no</td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malabsorption syndromes (celiac disease or cystic fibrosis)</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment for general malnutrition or specific deficits resulting in coagulation or other defects; with appropriate treatment, these deficits can be treated adequately to permit normal activities.</td>
</tr>
<tr>
<td>Short-bowel syndrome or other disorders requiring specialized nutritional support, including parenteral or enteral nutrition</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment for collision, contact, or limited-contact sports. Central or peripheral indwelling venous catheter might require special considerations for activities and emergency preparedness for unexpected trauma to the device(s).</td>
</tr>
<tr>
<td>Hepatitis, infectious (primarily hepatitis C)</td>
<td>Yes</td>
<td>All athletes should receive hepatitis B vaccination before participation. Because of the apparent minimal risk to others, all sports may be played as the athlete’s state of health allows. For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood.</td>
</tr>
<tr>
<td>Liver, enlarged</td>
<td>Qualified yes</td>
<td>If the liver is acutely enlarged, participation should be avoided because of risk of rupture. If the liver is chronically enlarged, individual assessment is needed before collision, contact, or limited-contact sports are played. Patients with chronic liver disease can have changes in liver function that affect stamina, mental status, coagulation, or nutritional status.</td>
</tr>
<tr>
<td>Diarrhea, infectious</td>
<td>Qualified no</td>
<td>Unless symptoms are mild and athlete is fully hydrated, no participation is permitted, because diarrhea can increase risk of dehydration and heat illness (see fever).</td>
</tr>
<tr>
<td><strong>GENITOURINARY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney, absence of one</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment for contact, collision, and limited-contact sports. Protective equipment can reduce risk of injury to the remaining kidney sufficiently to allow participation in most sports, providing such equipment remains in place during the activity.</td>
</tr>
<tr>
<td>Ovary, absence of one</td>
<td>Yes</td>
<td>Risk of severe injury to remaining ovary is minimal.</td>
</tr>
<tr>
<td>Pregnancy and postpartum period</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment. As pregnancy progresses, modifications to usual exercise routines become necessary; activities with high risk of falling or abdominal trauma should be avoided. Scuba diving and activities posing risk of altitude sickness should also be avoided during pregnancy. After the birth, physiologic and morphologic changes of pregnancy take 4-6 wk to return to baseline.</td>
</tr>
<tr>
<td>Testicle, undescended or absence of 1</td>
<td>Yes</td>
<td>Certain sports require a protective cup.</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Qualified yes</td>
<td>Athlete needs evaluation to assess functional capacity to perform sports-specific activity.</td>
</tr>
<tr>
<td>History of serious head or spine trauma or abnormality, including craniotomy, epidural bleeding, subdural hematoma, intracerebral hemorrhage, second-impact syndrome, vascular malformation, and neck fracture</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment. Research supports a conservative approach to concussion management, including no athletic participation while symptomatic or when deficits in judgment or cognition are detected. Followed by graduated return to full activity.</td>
</tr>
<tr>
<td>History of simple concussion (mild traumatic brain injury), multiple simple concussions, and/or complex concussion</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment. Risk of seizure during participation is minimal.</td>
</tr>
<tr>
<td>Recurrent headaches</td>
<td>Yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>Seizure disorder, well controlled</td>
<td>Yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of chronic alcohol use</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of head injury that required surgical intervention</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of soft tissue injury (injury to skin and underlying connective tissues, excluding bone)</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of arthroplasty or traumatic amputation</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of viral hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of active infectious hepatitis</td>
<td>Qualified no</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of infectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of viral hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of parasitic hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of viral hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of parasitic hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of viral hepatitis</td>
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<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of parasitic hepatitis</td>
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<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of viral hepatitis</td>
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<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
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<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of parasitic hepatitis</td>
<td>Qualified yes</td>
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<td>History of viral hepatitis</td>
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<tr>
<td>History of noninfectious hepatitis</td>
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<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of parasitic hepatitis</td>
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<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of viral hepatitis</td>
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<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of parasitic hepatitis</td>
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<tr>
<td>History of viral hepatitis</td>
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<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of parasitic hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of viral hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of parasitic hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of viral hepatitis</td>
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<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of noninfectious hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
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<tr>
<td>History of autoimmune hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>History of parasitic hepatitis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment.</td>
</tr>
<tr>
<td>CONDITION</td>
<td>MAY PARTICIPATE</td>
<td>EXPLANATION</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Seizure disorder, poorly controlled</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment for collision, contact, or limited-contact sports; The following noncontact sports should be avoided: archery, rifle, swimming, weightlifting, power lifting, strength training, and sports involving heights; in these sports, a seizure during activity can pose a risk to self or others</td>
</tr>
<tr>
<td>Recurrent plexopathy (burner or stinger) and cervical cord neurapraxia with persistent defects</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment for collision, contact, or limited-contact sports; regaining normal strength is an important benchmark for return to play</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary compromise, including cystic fibrosis</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment but, generally, all sports may be played if oxygenation remains satisfactory during graded exercise test; Athletes with cystic fibrosis need acclimatization and good hydration to reduce risk of heat illness</td>
</tr>
<tr>
<td>Asthma</td>
<td>Yes</td>
<td>With proper medication and education, only athletes with severe asthma need to modify their participation; For those using inhalers, recommend having a written action plan and using a peak flowmeter daily</td>
</tr>
<tr>
<td>Acute upper respiratory infection</td>
<td>Qualified yes</td>
<td>Athletes with asthma might encounter risks when scuba diving; Upper respiratory obstruction can affect pulmonary function; Athlete needs individual assessment for all except mild disease (see fever)</td>
</tr>
<tr>
<td><strong>RHEUMATOLOGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>Qualified yes</td>
<td>Athletes with systemic or polyarticular juvenile rheumatoid arthritis and history of cervical spine involvement need radiographs of C1 and C2 to assess risk of spinal cord injury; Athletes with systemic or HLA-B27–associated arthritis require cardiovascular assessment for possible cardiac complications during exercise For those with micrognathia (open bite and exposed teeth), mouth guards are helpful If uveitis is present, risk of eye damage from trauma is increased; ophthalmologic assessment is recommended In visually impaired athletes, guidelines for functionally 1-eyed athletes should be followed</td>
</tr>
<tr>
<td>Juvenile dermatomyositis, idiopathic myositis</td>
<td>Qualified yes</td>
<td>Athlete with juvenile dermatomyositis or systemic lupus erythematosus with cardiac involvement requires cardiology assessment before participation; Athletes receiving systemic corticosteroid therapy are at higher risk for osteoporotic fractures and avascular necrosis, which should be assessed before clearance; those receiving immunosuppressive medications are at higher risk for serious infection. Sports activities should be avoided when myositis is active. Rhabdomyolysis during intensive exercise can cause renal injury in athletes with idiopathic myositis and other myopathies. Because of photosensitivity with juvenile dermatomyositis and systemic lupus erythematosus, sun protection is necessary during outdoor activities. With Raynaud phenomenon, exposure to the cold presents risk to hands and feet</td>
</tr>
<tr>
<td>Systemic lupus erythematosus Raynaud phenomenon</td>
<td>Qualified yes</td>
<td></td>
</tr>
<tr>
<td><strong>SICKLE CELL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Qualified yes</td>
<td>Athlete needs individual assessment; In general, if illness status permits, all sports may be played; however, any sport or activity that entails overexertion, overheating, dehydration, or chilling should be avoided Participation at high altitude, especially when not acclimatized, also poses risk of sickle cell crisis</td>
</tr>
<tr>
<td>Sickle cell trait</td>
<td>Yes</td>
<td>Athletes with sickle cell trait generally do not have increased risk of sudden death or other medical problems during athletic participation under normal environmental conditions; however, when high exertional activity is performed under extreme conditions of heat and humidity or increased altitude, such catastrophic complications have occurred rarely Athletes with sickle cell trait, like all athletes, should be progressively acclimatized to the environment and to the intensity and duration of activities and should be sufficiently hydrated to reduce the risk of exertional heat illness and/or rhabdomyolysis According to National Institutes of Health management guidelines, sickle cell trait is not a contraindication to participation in competitive athletics, and there is no requirement for screening before participation More research is needed to fully assess potential risks and benefits of screening athletes for sickle cell trait</td>
</tr>
</tbody>
</table>

This table is intended for use by medical and nonmedical personnel. “Needs evaluation” means that a physician with appropriate knowledge and experience should assess the safety of a given sport for an athlete with the listed medical condition. Unless otherwise noted, this need for special consideration is because of variability in the severity of the disease, the risk of injury for the specific sports, or both.

### Figure 686-1 Classification of sports according to cardiovascular demands (based on combined static and dynamic components).

This classification is based on peak static and dynamic components achieved during competition. The higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake (Max O₂) achieved and results in increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction (MVC) reached and results in increasing blood pressure load. Activities with the lowest total cardiovascular demands (cardiac output and blood pressure) are shown in box IA, and those with the highest demands are shown in box IIC. Boxes IIA and IB depict activities with low to moderate total cardiovascular demands; boxes IIA, IIB, and IIC depict activities with moderate total cardiovascular demands; and boxes IIB and IIC depict high-moderate total cardiovascular demands. These categories progress diagonally across the graph from lower left to upper right. *Danger of bodily collision.* *Increased risk if syncope occurs. Participation is not recommended by the American Academy of Pediatrics.* *The American Academy of Pediatrics classifies cricket in the IB box (low static component and moderate dynamic component).* (From Mitchell JH, Haskell W, Snell P, et al: 36th Bethesda conference. Task force 8: classification of sports. J Am Coll Cardiol 45:1364–1367, 2005.)

#### Table 686-3 Activities and cardiovascular demands

<table>
<thead>
<tr>
<th>Classification</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA (Low)</td>
<td>Billiards, Bowling, Cricket, Curling, Golf, Riffery</td>
</tr>
<tr>
<td>IIA (Moderate)</td>
<td>Archery, Auto racing, Diving, Equestrian, Motorcycling</td>
</tr>
<tr>
<td>IIB (High moderate)</td>
<td>American football, Field events (jumping) Figure skating, Field hockey, Ice hockey, Listening (skating technique) Locale, Running (middle distance), Swimming, Team handball</td>
</tr>
<tr>
<td>IIC (High)</td>
<td>Boxing, Cross-country skiing, (skating technique) Locale, Running (long distance), Soccer, Tennis</td>
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<table>
<thead>
<tr>
<th>Classification</th>
<th>Activities</th>
</tr>
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<tbody>
<tr>
<td>A. Low (&lt;40% Max O₂)</td>
<td>Bobsledging/luge, Field events (throwing), Gymnastics, Martial arts, Sailing, Sport climbing, Water skiing, Weight lifting, Wind surfing</td>
</tr>
<tr>
<td>B. Moderate (40-70% Max O₂)</td>
<td>Body building, Downhill skiing, Ice skating, Skateboarding, Snowboarding, Wrestling</td>
</tr>
<tr>
<td>C. High (&gt;70% Max O₂)</td>
<td>Boxing, Canoeing/kayaking, Cycling, Decathlon, Rowing, Speed skating, Triathlon, Triathlon</td>
</tr>
</tbody>
</table>

**in retrospect** there were preceding symptoms of dizziness, chest pain, syncope, palpitations, shortness of breath, and/or a family history of early, unexpected death. Chest radiographs, electrocardiograms, and echocardiograms are not recommended as routine screening tests. If there is a **suspicion** of heart disease, such as a history of syncope, presyncope, palpitations, or excessive dyspnea with exercise, or a family history of a condition such as hypertrophic cardiomyopathy or prolonged QT or Marfan syndrome, the evaluation should be complete and include a 12-lead electrocardiogram, an echocardiogram, Holter or event-capture monitoring, and a stress test with electrocardiographic monitoring. Recommendations for participation with identified cardiac disease should be made in consultation with a cardiologist.

**Disqualification and limitations** for sports participation among various medical conditions are available from the American Academy of Pediatrics (see Table 686-3). Sports may also be classified by intensity (Fig. 686-1) and contact (Table 686-4). Athletes may seek to participate in sports against medical advice and have done so successfully for professional sports. Section 504(a) of the Rehabilitation Act of 1973 prohibits discrimination against disabled athletes if they have the capabilities or skills required to play a competitive sport. This was reinforced through the Americans with Disabilities Act of 1990. An amateur athlete has no absolute right to decide whether to participate in competitive sports. Participation in competitive sports is considered a privilege, not a right. *Knapp v Northwestern University* established that "difficult medical decisions involving complex medical problems can be made by responsible physicians exercising prudent judgment (which will be necessarily conservative when definitive scientific evidence is lacking or conflicting) and relying on the recommendations of specialist consultants or guidelines established by a panel of experts."

Bibliography is available at Expert Consult.
Bibliography


<table>
<thead>
<tr>
<th>CONTACT OR COLLISION</th>
<th>NONCONTACT</th>
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<tbody>
<tr>
<td>Basketball</td>
<td>Archery</td>
</tr>
<tr>
<td>Boxing*</td>
<td>Badminton</td>
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<tr>
<td>Diving</td>
<td>Body building</td>
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<tr>
<td>Field hockey</td>
<td>Bowling</td>
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<tr>
<td>Football, tackle</td>
<td>Canoeing or kayaking (flat water)</td>
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<tr>
<td>Ice hockey†</td>
<td>Crew or rowing</td>
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<tr>
<td>Lacrosse</td>
<td>Curling</td>
</tr>
<tr>
<td>Martial arts</td>
<td>Dancing</td>
</tr>
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<td>Rodeo</td>
<td>• Ballet</td>
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<tr>
<td>Rugby</td>
<td>• Modern</td>
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<tr>
<td>Ski jumping</td>
<td>• Jazz</td>
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<tr>
<td>Soccer</td>
<td>Field events</td>
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<tr>
<td>Team handball</td>
<td>• Discus</td>
</tr>
<tr>
<td>Water polo</td>
<td>• Javelin</td>
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<tr>
<td>Wrestling</td>
<td>• Shot put</td>
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<tr>
<td></td>
<td>Golf</td>
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<tr>
<td></td>
<td>Orienteering†</td>
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<td></td>
<td>Power lifting</td>
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<td>Race walking</td>
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<td>Riffery</td>
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<td>Scuba diving</td>
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<td>Swimming</td>
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<td>Table tennis</td>
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<td>Tennis</td>
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<td>Track</td>
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<td></td>
<td>Weight lifting</td>
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<table>
<thead>
<tr>
<th>LIMITED CONTACT</th>
<th>LIMITED CONTACT</th>
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<tbody>
<tr>
<td>Baseball</td>
<td>Archery</td>
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<tr>
<td>Bicycling</td>
<td>Badminton</td>
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<tr>
<td>Cheerleading</td>
<td>Body building</td>
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<tr>
<td>Canoeing or kayaking (white water)</td>
<td>Bowling</td>
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<tr>
<td>Fencing</td>
<td>Canoeing or kayaking (flat water)</td>
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<tr>
<td>Field events</td>
<td>Crew or rowing</td>
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<tr>
<td>• High jump</td>
<td>Curling</td>
</tr>
<tr>
<td>• Pole vault</td>
<td>Dancing</td>
</tr>
<tr>
<td>Floor hockey</td>
<td>• Ballet</td>
</tr>
<tr>
<td>Football, flag</td>
<td>• Modern</td>
</tr>
<tr>
<td>Gymnastics</td>
<td>• Jazz</td>
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<tr>
<td>Handball</td>
<td>Field events</td>
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<tr>
<td>Horseriding</td>
<td>• Discus</td>
</tr>
<tr>
<td>Racquetball</td>
<td>• Javelin</td>
</tr>
<tr>
<td>Skating</td>
<td>• Shot put</td>
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<tr>
<td>• Ice</td>
<td>Golf</td>
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<tr>
<td>• Inline</td>
<td>Orienteering†</td>
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<tr>
<td>• Roller</td>
<td>Power lifting</td>
</tr>
<tr>
<td>Skiing</td>
<td>Race walking</td>
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<tr>
<td>• Cross-country</td>
<td>Riffery</td>
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<tr>
<td>• Downhill</td>
<td>Rope jumping</td>
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<tr>
<td>• Water</td>
<td>Running</td>
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<td></td>
<td>Weight lifting</td>
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</table>

*Participation not recommended by the American Academy of Pediatrics.
†The American Academy of Pediatrics recommends limiting the amount of body checking allowed for hockey players ≤15 yr to reduce injuries.
‡A race (contest) in which competitors use a map and compass to find their way through unfamiliar territory.

Most sprains are grades I-III. A grade I sprain is defined as mild damage to a ligament or ligaments without instability of the affected joint. A grade II sprain is considered a partial tear to the ligament, stretched to the point that it becomes loose. Grade III is a complete tear of the ligament with instability to the affected joint. A strain is an injury to a muscle or tendon and these, too, are graded I-III. Grade I muscle strains involve disruption of only a few muscle fibers, pain is mild to moderate and range of motion and strength are at or near normal. Grade II strains represent a more significant partial tear of the muscle and frequently involve loss of range of motion and strength. Grade III strains are defined as complete rupture of the musculotendinous unit. A contusion is a crush injury to any soft tissue. The history of the injury is especially helpful in assessing musculoskeletal trauma. More severe injuries, indicating internal derangement, can have acute signs and symptoms such as immediate swelling, deformity, numbness or “give-way” weakness, a loud painful pop, mechanical locking of the joint, or instability.

**Overuse Injuries**

Overuse injuries are caused by repetitive microtrauma that exceeds the body’s rate of repair. This occurs in muscles, tendons, bone, bursae, cartilage, and nerves. Overuse injuries occur in all sports but more commonly in sports emphasizing repetitive motion (swimming, running, tennis, and gymnastics). Factors can be categorized into extrinsic (training errors, poor equipment or workout surface) and intrinsic (athlete’s anatomy or medical conditions). Training error is the most commonly identified factor. At the beginning of the workout program, athletes might violate the 10% rule: Do not increase the duration or intensity of workouts more than 10% per week. Intrinsic factors include abnormal biomechanics (leg-length discrepancy, pes planus, pes cavus, tarsal coalition, valgus heel, external tibial torsion, and femoral anteversion), muscle imbalance, inflexibility, and medical conditions (deconditioning, nutritional deficits, amenorrhea, and obesity). The athlete should be asked about the specifics of training. Runners should be asked about their shoes, orthotics, running surface, weekly mileage or time spent running per week, speed or hill workouts, and previous injuries and rehabilitation. When causative factors are identified, they can be eliminated or modified so that after rehabilitation the athlete does not return to the same regimen and suffer reinjury.

For athletes engaged in excessive training that causes an overuse injury (e.g., multiple-sport school athletes), curtailing all exercise may not be necessary. Treatment is a reduction of training load (relative rest) combined with a rehabilitation program designed to return athletes to their sport as soon as possible while minimizing exposure to reinjury. Early identification of an overuse injury requires less alteration of the workout regimen.

The goals of treatment are to control pain and spasm to rehabilitate flexibility, strength, endurance, and proprioceptive deficits (Table 687-1). In many overuse injuries, the role of inflammation in the process is minimal. For most injuries to tendons, the term tendinitis is obsolete because there is little or no inflammation on histopathology of tendons. Instead, there is evidence of microscopic trauma to the tissue. Most of these entities are now more appropriately called tendinosis and, when the tendon tissue is scarred and very abnormal, tendinopathy. With tendinosis, there is less of a role for antiinflammatory medication in the treatment, except as an analgesic.

**INITIAL EVALUATION OF THE INJURED EXTREMITY**

Initially, the examiner should determine the quality of the peripheral pulses and capillary refill rate as well as the gross motor and sensory function to assess for neurovascular injury. The first priorities are to maintain vascular and skeletal stability.

Criteria for immediate attention and rapid orthopedic consultation include vascular compromise, nerve compromise, and open fracture. The exposed wound should be covered with sterile saline-soaked gauze, and the injured limb should be padded and splinted. Pressure should
Table 687-1  Staging of Overuse Injuries

<table>
<thead>
<tr>
<th>GRADE</th>
<th>GRADING SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pain only after activity</td>
<td>Modification of activity, consider cross-training, home rehabilitation program</td>
</tr>
<tr>
<td></td>
<td>Does not interfere with performance or intensity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generalized tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disappears before next session</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Minimal pain with activity</td>
<td>Modification of activity, cross-training, home rehabilitation program</td>
</tr>
<tr>
<td></td>
<td>Does not interfere with performance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More localized tenderness</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Pain interferes with activity and performance</td>
<td>Significant modification of activity, strongly encourage cross-training, home rehabilitation program, and outpatient physical therapy</td>
</tr>
<tr>
<td></td>
<td>Definite area of tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually disappears between sessions</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Pain with activities of daily living</td>
<td>Discontinue activity temporarily, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy</td>
</tr>
<tr>
<td></td>
<td>Pain does not disappear between sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked interference with performance and training intensity</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Pain interferes with activities of daily living</td>
<td>Prolonged discontinuation of activity, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy</td>
</tr>
<tr>
<td></td>
<td>Signs of tissue injury (e.g., edema)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic or recurrent symptoms</td>
<td></td>
</tr>
</tbody>
</table>

be applied to any site of bleeding. Additional criteria include deep laceration over a joint, unreducible dislocation, grade III (complete) tear of a muscle–tendon unit, and displaced, significantly angulated fractures (depends on the bone involved, the degree of displacement and angulation, and neurovascular status of the extremity).

**TRANSITION FROM IMMEDIATE MANAGEMENT TO RETURN TO PLAY**

Rehabilitation of a musculoskeletal injury should begin on the day of the injury.

**Phase 1**

Limit further injury, control swelling and pain, and minimize strength and flexibility losses. **PRICE** principles (Protection, Rest, Ice, Compression, and Elevation) need to be applied. Crutches, air stirrups for ankle sprains, slings for arm injuries and elastic wraps (4-8 inches) for compression are a helpful inventory of office supplies. Ice can be placed directly over the injury as tolerated for 20 min continuously 3-4 times per day until the swelling resolves. Compression limits further bleeding and swelling but should not be so tight that it limits perfusion. Elevation of the extremity promotes venous return and limits swelling. A nonsteroidal antiinflammatory drug or acetaminophen is indicated for analgesia.

Pain-free isometric strengthening and range of motion should be initiated as soon as possible. Pain inhibits full muscle contraction; deconditioning results if the pain and resultant nonuse persist for days to weeks, thus delaying recovery. Education about the nature of the injury and the specifics of rehabilitation exercises, including handouts with written instructions and drawings demonstrating the exercises, are helpful.

**Phase 2**

Improve strength and range of motion (i.e., flexibility) while allowing the injured structures to heal. Protective devices are removed when the patient's strength and flexibility improve and activities of daily living are pain free. Flexibility can then be improved by a program of specific stretches, held for 15-30 sec for 3-5 repetitions, once or twice daily. A physical therapist or athletic trainer is invaluable in guiding the athlete through this process. Protective devices might need to be used for months during sports participation. Swimming, water jogging, and stationary cycling are good aerobic exercises that can allow the injured extremity to get relative rest or be used pain free while maintaining cardiovascular fitness.

**Phase 3**

Achieve near-normal strength and flexibility of the injured structures and further improve or maintain cardiovascular fitness. Strength and endurance are improved under controlled conditions using elastic bands and eventually exercise equipment followed by free weights. Sensory proprioceptive training allows the athlete to redevelop the kinesthetic sense critical to joint function and stability.

**Phase 4**

Return to exercise or competition without restriction. When the athlete has reached nearly normal flexibility, strength, proprioception, and endurance, the athlete can start sports-specific exercises. The athlete will make the transition from the rehabilitation program to functional rehabilitation appropriate for the sport. Substituting sports participation for rehabilitation is inappropriate; rather, there should be progressive stepwise functional return to a full activity or play program. For instance, a basketball player recovering from an ankle injury might begin a walk-run-sprint-cut program before returning to competition. At any point in this progression, if pain is experienced, the athlete needs to stop, apply ice, avoid running for 1-2 days, continue to do ankle exercises, and then resume running at a lower intensity and progress accordingly.

**Relative Rest and Return-to-Play Guidelines**

Relative rest means that the athlete can do whatever the athlete wants as long as the injured structures do not hurt during or within 24 hr of the activity. Exercising beyond the pain threshold delays recovery.

**DIFFERENTIAL DIAGNOSES OF MUSCULOSKELETAL PAIN**

Traumatic, rheumatologic, infectious, hematologic, psychologic, congenital, and oncologic processes can cause the presenting complaint of musculoskeletal pain. Symptoms such as fatigue, weight loss, rash, multiple joint complaints, fever, chronic or recent illness, and persistent pain despite conservative care suggests a diagnosis other than sports-related trauma. The possibility of child abuse as an etiology is not to be overlooked permeating all socioeconomic strata. Incongruity between the patient's history and physical examination findings should lead to further evaluation. A negative review of systems with an injury history consistent with the physical findings suggests a sports-related etiology.

*Bibliography is available at Expert Consult.*
Bibliography
687.1 Growth Plate Injuries

Kevin P. Murphy and Aaron M. Karlin

Approximately 20% of pediatric sports injuries seen in the emergency department are fractures, and 25% of those fractures involve an epiphyseal growth plate or physis (see Chapter 683). Growth in long bones occurs in 3 areas and is susceptible to injury. Immature bone can be acutely injured at the physis (Salter-Harris fractures, see Chapter 683.2), the articular surface (osteochondritis dissecans), or the apophysis (avulsion fractures). Boys suffer about twice as many physeal fractures as girls; the peak incidence of fracture is during peak height velocity (girls: age 12 ± 2.5 yr; boys: age 14 ± 2 yr). The physis is a pressure growth plate and is responsible for longitudinal growth in bone. The apophysis is a bony outgrowth at the attachment of a tendon and is a traction physis. The epiphysis is the end of a long bone, distal or proximal to the long bone, and contains articular cartilage at the joint.

Physeal injuries of the distal radius occur most often in the growing child or adolescent resulting from excessive force applied to the upper extremity. Injuries of this nature can be seen in athletes including those participating in gymnastics, cheerleading, ice skating, hockey and weight lifting. Mechanisms of injury include falls onto an outstretched hand or repetitive dorsiflexion and axial loading through the distal radius (see Chapter 693). Chronic wrist pain can be seen in up to 79% of young gymnasts, particularly female gymnasts between the ages of 12 and 14 yr. With repetitive axial loading temporary metaphyseal ischemia may be induced preventing cartilage calcification and causing the physis to widen. With widening of the distal radial physis, microfractures can develop. Clinical features involve radial wrist pain particularly dorsal with passive and active hyperextension activities relieved with suspension of the offending activity. Tenderness or focal pain around the circumference of the distal radius is often noted. Differential diagnosis includes metacarpal fractures, scaphoid fracture and in the older child, De Quervain tenosynovitis. Juvenile idiopathic arthritis always needs to be considered in a child with a painful swollen wrist not to exclude malignancy or an infectious process. X-rays of the wrist can be helpful particularly when compared to the contralateral extremity. Radiographs can show physeal widening with cystic changes involving the metaphyseal segment, beaking of the distal epiphyseal and in later stages, positive ulnar variance. Bone scan may be helpful for stress fractures followed by MRI if subsequently needed. PRICE principles are followed with nonnarcotic pain management. Salter-Harris fractures types I and II can be treated with closed reduction and immobilization. Ulnar shortening osteotomy may be necessary in the athlete with significant ulnar positive variance. Physeal injuries at the knee (distal femur, proximal tibia) are rare. Growth disturbance following a growth plate injury is a function of location and the part of the physis fractured. These factors influence the probability a physeal bar will form, resulting in growth arrest. The areas making the largest contribution to longitudinal growth in the upper extremities are the proximal humerus and distal radius and ulna; in the lower extremities, they are the distal femur and the proximal tibia and fibula. Injuries to these areas are more likely to cause growth disturbance compared with physeal injuries at the other end of these long bones. The type of the physis fracture relative to risk of growth disturbance is described by the Salter-Harris classification system (see Table 683-1). A grade I injury is least likely to result in growth disturbance, and grade V is the most likely fracture to result in growth disturbance.

Osteochondritis dissecans (OCD) affects the subchondral bone and overlying articular surface (see Chapter 683). With avascular necrosis of subchondral bone, the articular surface can flatten, soften, or break off in fragments. The etiology is unknown but may be related to repetitive stress injury in some patients. The condition most commonly affects the knee (lateral aspect of the medial femoral condyle in 70% of patients and lateral femoral condyle in 20%) with the patella in 10%. Other joints where OCD lesions are also seen are the ankle (talus), elbow (usually involving the capitellum), and radial head. OCD classically affects athletes in their 2nd decade. The most common presentation is poorly localized vague knee pain. There is rarely a history of recent acute trauma. Some OCD lesions are asymptomatic (diagnosed on “routine” radiographs), whereas others are manifested as joint effusion, pain, decreased range of motion, and mechanical symptoms (locking, popping, catching). Activity usually worsens the pain.

Physical examination might show no specific findings. Sometimes tenderness over the involved condyle can be elicited by deep palpation with the knee flexed. Diagnosis is usually made with plain radiographs (Fig. 687-1). A tunnel view radiograph can be obtained to better view the posterior two-thirds of the femoral condyle. Treatment of OCD remains controversial. Intact lesions can often be treated symptomatically with or without activity modification or immobilization. Free fragments often require surgical removal. Drilling techniques can be utilized and are helpful in stimulating new bone formation, healing, and return of mobile bodies to their original donor sites. Long-term sequelae can be seen in up to 25% with atypical lesions, older age, effusion, and lesions of large size.

Avulsion fractures occur when a forceful muscle contraction dislodges the apophysis from the bone. They occur most commonly around the hip (Fig. 687-2) and are treated nonsurgically. Acute fractures to other apophyses (knee and elbow) require urgent orthopedic consultation. Chronically increased traction at the muscle–apophysis attachment can lead to repetitive microtrauma and pain at the apophysis. The most common areas affected are the knee (Osgood-Schlatter and Sinding-Larsen-Johansson disease), the ankle (Sever disease) (Fig. 687-3), and the medial epicondyle (Little League elbow). Traction apophysitis of the knee and ankle can potentially be treated in a primary care setting. The main goal of treatment is to minimize the intensity and incidence of pain and disability. Exercises that increase the strength, flexibility, and endurance of the muscles attached at the

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Figure 687-1 Osteochondritis dissecans in the elbow. (From Anderson SJ: Sports injuries. Curr Probl Pediatr Adolesc Health 35:105–176, 2005.)
apophysis, using the relative rest principle, are appropriate. Symptoms can last for 12-24 mo if untreated. As growth slows, symptoms abate.

Bibliography is available at Expert Consult.

687.2 Shoulder Injuries
Kevin P. Murphy and Aaron M. Karlin

Shoulder pain associated with radiating symptoms down the arm should raise the possibility of a neck injury. Neck pain and tenderness or limitation of cervical range of motion requires that the cervical spine be immobilized and that the athlete be transferred for further evaluation. If there is no neck pain or tenderness or limitation of motion of the cervical spine, then the shoulder is likely the site of the primary injury.

CLAVICLE FRACTURES
Clavicle fracture is one of the most common shoulder injuries. Injury is usually sustained by a fall on the lateral shoulder, on an outstretched hand, or by direct blow. Approximately 80% of fractures occur in the middle third of the clavicle. With younger children, plastic bowing of the clavicle may be present instead of an overt fracture and should be treated in the same fashion. Treatment is conservative and includes the use of an arm sling for comfort and protection. Healing time is shorter in comparison to adults, generally 4-6 wk. And additional 2-3 wk period of protection from contact/collision activities is recommended after clinical and radiographic healing is achieved to prevent reinjury. If nondisplaced, most medial and lateral clavicular fractures can be managed similar to middle 3rd clavicular fractures. Displaced lateral and medial third fractures require orthopedic consultation because of a higher incidence of acromioclavicular osteoarthritis (lateral) and physeal involvement (medial). Distal clavicular osteolysis is likely an overuse injury associated with slow dissolution and resorption of bone. The cause of injury is unclear, appearing most consistent with a stress reaction or fracture at the site of considerable force. This lesion is commonly seen in weightlifting athletes and can be seen in the older children. Nonoperative treatment including activity limitations, ice, nonsteroidal antiinflammatory agents and cortisone injections can be helpful. Gripping the bar at a greater distance for the weightlifter may be helpful. For those not willing to modify weightlifting activity or with persistent symptoms despite conservative care, surgery can be very successful and involves removal of the distal clavicle (approximately 1 cm) with no loss of strength and full return to activity anticipated.

ACROMIOCLAVICULAR SEPARATION
An acromioclavicular (AC) separation most commonly occurs when an athlete sustains a direct blow to the acromion with the humerus in an adducted position, forcing the acromion inferiorly and medially. Force is directed toward the AC and coracoclavicular ligaments because of the inherent stability of the sternoclavicular joint. Patients have point tenderness at the AC joint, pain with lifting their arms above the level of their shoulder, and may have an apparent step-off between the distal clavicle and the acromion (Fig. 687-4).

Type I AC injuries involve isolated sprain of the AC ligament with the periosteal sleeve intact. There is no visible deformity and radiographs are normal. Pain is elicited with adduction of the humerus across the chest. Type II injuries involve the AC ligament and coracoclavicular ligament, as well as partial disruption of the periosteal sleeve. Radiographs may show slight widening of the AC joint though the distance between the clavicle and the coracoid process is unchanged in comparison to the uninjured shoulder. Treatment of type I and type II AC injuries is conservative and nonoperative and consists of ice, nonsteroidal antiinflammatory agents and a sling for immobilization and pain control acutely. Shoulder range of motion exercises and strengthening of the rotator cuff, deltoid and trapezius musculature are incorporated early in the course once pain free range improves to prevent residual joint stiffness. A short course of physical therapy may be helpful if range of motion limitations are present 2-4 wk out from
Bibliography


ANTERIOR DISLOCATION
The most common mechanism of injury is making contact with another player with the shoulder abducted to 90 degrees and forcefully rotated externally. A common example of the latter is a football player tackling another player only with the arm. Patients complain of severe pain and that their shoulder “popped out of place” or “shifted.” Patients with an unreduced anterior dislocation have a hollow region inferior to the acromion and a bulge in the anterior portion of the shoulder caused by anterior displacement of the humeral head. Abnormal sensation of the lateral deltoid region (axillary nerve) and the extensor surface of the proximal forearm (musculocutaneous nerve) should be noted.

Reduction of a dislocated shoulder should be made expeditiously assuming no presence of crepitans (concerning for fracture). Numerous safe methods for closed reduction have been described, including the traction–counter traction technique, the Stimson maneuver, and the abduction maneuver. Postreduction radiographs are helpful and may show evidence of a posterior lateral humeral head impaction fracture (Hill-Sachs lesion). Injuries to the surrounding soft tissues, including the anterior capsule and labrum, are best evaluated by MRI, often with an accompanying arthrogram of the glenohumeral joint.

Once reduced, initial treatment of a dislocation includes placing the patient into an arm sling for comfort and protection. The duration of immobilization is controversial and may last anywhere from a few days to 4-6 wk. The most significant risk after an acute traumatic dislocation is recurrence. Most sports medicine practitioners encourage early range of motion and strengthening exercises as tolerated. Rehabilitation focuses upon progressive strengthening of the rotator cuff, deltoid, and periscapular muscles at increasing degrees of abduction and external rotation. Strengthening of the rotator cuff muscles is extremely important as they are the dynamic stabilizers of the glenohumeral joint, integral in preventing future dislocation. Plyometric exercises may also be incorporated near the end of rehabilitation to improve proprioceptive function in preparation for return to athletics. Patients can return to play when strength, flexibility, and proprioception are equal to the uninjured shoulder to the extent that they are able to protect the shoulder and perform sports specific activities without pain. Surgery is to be considered in cases of multiple recurrent dislocations or in those individuals that fail to heal adequately after prolonged rehabilitation. Additionally, early operative repair should be considered for athletes participating in contact or collision spots that inherently have higher recurrence rates.

ROTATOR CUFF INJURY
The rotator cuff muscles comprise the supraspinatus, infraspinatus, teres minor, and subscapularis. The function of these muscles is to rotate the humerus and stabilize the humeral head against the glenoid. The supraspinatus is most commonly injured, an acute strain caused by trauma or chronic tendinosis from overuse. Specifically, rotator cuff tendinosis commonly presents with complaint of pain with overhead arc of motion, such as with throwing, lifting, or reaching for objects above one’s head. Pain is often poorly localized about the shoulder, although may be referred to the deltoid. Onset of pain is often insidious and commonly associated with increased frequency or duration of overhead throwing or lifting activities. Pain is exacerbated with these or other activities but is often present at rest; nighttime pain in more severe cases. On exam, manual muscle testing of the cuff muscles often produces pain and in some cases weakness in comparison to the uninjured shoulder. Supraspinatus tendinosis produces pain with active abduction against resistance in which the patient abducts the arm to 90 degrees, forward flexes to 30 degrees anterior to the parasagittal plane, and internally rotates the humerus.

Treatment of rotator cuff tendinosis includes relative rest from athletics or activities causing pain, ice, analgesia or nonsteroidal anti-inflammatory use. Strengthening of the rotator cuff and scapular stabilizer musculature, modifications of technique, and core strengthening are important components of rehabilitation often supervised by a physical therapist. In the young athlete, rotator cuff pain is most commonly a result of glenohumeral instability and not rotator cuff impingement syndrome, more commonly seen in adults and caused by impingement of the rotator cuff by the bony structures superior to it. As a result, treatment focusing on stretching alone can make symptoms worse. Return to play often includes gradual increases in load placed upon the rotator cuff as the patient resumes their prior activities such as an interval throwing program in baseball.

Glenoid labrum tears may present in similar insidious fashion to rotator cuff tendinosis or be associated with an acute traumatic dislocation. This is frequently manifested with pain in the glenohumeral joint.
and may be associated with a sensation of clicking or catching in the shoulder. This can frequently be reproduced on exam. One of the most common lesions is a superior labrum anterior and posterior lesion. Throwing athletes are at particular risk. Mechanism of injury is thought to be related to a traction injury along the long head of the biceps at its attachment at the superior glenoid labrum occurring during a throwing cycle. Radiographs are usually normal. MRI with arthrogram is the best study to identify glenoid labrum pathology.

**Proximal humeral stress fracture** (epiphysiodesis) is an uncommon cause of proximal shoulder pain and is suspected when shoulder pain does not respond to routine measures. Gradual onset of deep shoulder pain occurs in a young (open epiphyseal plates) athlete involved in repetitive overhead motion, such as in baseball, tennis, or swimming, but with no history of trauma. Tenderness is noted over the proximal humerus; the diagnosis is confirmed by detecting a widened epiphyseal plate on plain radiographs, increased uptake on nuclear scan, or edema of the physis on MRI. Treatment is total rest from throwing for 6–8 wk.

Non–sports-related conditions that need to be considered in the child with a painful shoulder include the Sprengel deformity. This deformity involves the scapula, which fails to descend from its cervical region overlying the 1st through 5th ribs. Children often present with a shortened neckline and lack of normal scapular thoracic motion. Malpositioning of a glenoid can cause limited forward flexion and abduction of the shoulder. An omovertebral bar is present in up to 50% of cases. This bar connects the superior medial angle of the scapula and the cervical spine and consists of fibrous cartilaginous tissue or bone. Other regional abnormalities can include scoliosis with a prominent scapula on the convex side, rib anomalies, and Klippel–Feil syndrome. Winging of the scapula always raises the question of muscular dystrophy, particularly scapular thoracic. Family histories can be most helpful. Primary bone tumors (see Chapter 501) common to the upper extremities include Ewing sarcoma of the scapula and osteogenic sarcoma of the proximal humerus, in addition to osteoblastomas and chondroblastomas common to the diaphysis and epiphysis of long bones. The most common presenting manifestations of osteosarcoma are pain, upper limb dysfunction, and swelling. Similar presentations can be seen in Ewing sarcoma, along with weight loss and fever. Symptoms not responding to conservative treatment require further investigation and specialist consultation.

Bibliography is available at Expert Consult.

### 687.3 Elbow Injuries

**Kevin P. Murphy and Aaron M. Karlin**

#### ACUTE INJURIES

The most commonly dislocated joint in childhood is the elbow. Radial head subluxation, or “nurse maid’s elbow,” comprises the majority of these and is discussed in more depth in Chapter 681. Posterior dislocation is the next most common type of elbow dislocation, with its mechanism being that of falling backward onto an outstretched arm with the elbow in extension. The dislocation may be complete or incomplete, termed “perched,” with the trochlea subluxed upon the top of the coronoid process. The ulnar collateral ligament is commonly disrupted along with other components of the soft-tissue capsule about the elbow. Fractures of the olecranon (greater than 80%) or medial epicondyile may be present as well. An obvious deformity is visualized with the olecranon process displaced prominently behind the distal humerus. Careful examination of the distal radius and ulnar pulses to assess vascular integrity of the distal upper arm is important because of the potential for injury to the brachial artery. Sensation to the distal extremity should also be assessed because of possible injury to the radial, median, and ulnar nerves. Reduction should be performed as soon as possible before significant swelling and muscle spasm potentially complicate the procedure. Longitudinal traction is applied to the forearm with gentle upward pressure on the distal humerus so that the coronoid process clears the trochlea. If reduction is unable to be performed, the arm should be placed in a padded splint and the patient transported to an emergency facility. Supracondylar humeral fractures can result from the same mechanism of injury as elbow dislocations and can be difficult to distinguish from a posterior dislocation because of significant swelling about the elbow joint. These, too, can be complicated by concomitant injury to the brachial artery and to a lesser extent the median, radial, and ulnar nerves. The injury typically occurs in the 1st decade of life, which is associated with peak hyperlaxity of the elbow joint in children between the ages of 5 and 8 yr. An acute compartment syndrome can develop after these fractures, which is associated with a fat pad sign (Fig. 687-5). These fractures should be referred for orthopedic consultation and are discussed in more depth in Chapter 683.

Direct trauma to the elbow can cause bleeding and inflammation in the olecranon bursa resulting in olecranon bursitis. Aspiration is rarely required and this injury can be managed with ice, compressive dressing and analgesia (RICE principles). An overlying elbow pad provides comfort during activity and prevention of re-injury.

#### Chronic Injuries

Overuse injuries occur primarily in throwing sports and sports that require repetitive wrist flexion or extension or demand weightbearing on hands (gymnastics). “Little League elbow” is a broad term for several different elbow problems.

**Throwing overhand** creates valgus stress to the elbow with medial opening of the joint and lateral compressive forces.

**Medial elbow pain** is a common complaint of young throwers, resulting from repetitive valgus overload of the wrist flexor-pronator muscle groups and their attachment on the medial apophysis. In preadolescents who still have maturing secondary ossification centers,
Bibliography

traction apophysitis of the medial epicondyle is likely. Patients have tenderness along the medial epicondyle; pain is exacerbated by valgus stress or resisted wrist flexion and pronation. Wrist pain may be present in more severe cases. Radiographs may show widening of the growth plate at the medial apophysis in comparison to the uninjured elbow. Treatment includes no throwing for 4-6 wk, pain-free strengthening, and stretching of the flexor–pronator group followed by a 1-2 wk progressive functional throwing program with careful rehabilitation. Incorporation of core strengthening and scapular stabilizing exercise, as well as addressing proper throwing mechanics (to reduce the load upon the medial elbow), are important components of rehabilitation. This problem has to be treated with rest because of the risk of nonunion of the apophysis and chronic pain. If pain occurs acutely, avulsion fracture of the medial epicondyle must be considered. Radiographs should be taken in any thrower with acute elbow pain (Fig. 687-6). If the medial epicondyle is avulsed, orthopedic consultation is indicated.

In older adolescents and young adults with a fused apophysis, the vulnerable structure is the ulnar collateral ligament (UCL). UCL sprains/tears are common in sports requiring high-velocity throwing or overhead activities. Medial elbow pain primarily worse during the acceleration phase of throwing is common. A sensation of elbow “opening” during throwing is also frequently described. On exam focal tenderness to palpation over the UCL is present. Additionally laxity may be appreciated with valgus stress of the elbow when flexed to 30 and/or 90 degrees. Radiographs are generally unremarkable. MRI with arthrography or ultrasonography is often necessary to assess the integrity of the UCL. Partial tears can be treated with a period of time off from throwing (2-4 wk) followed by careful progressive rehabilitation as discussed above for medial elbow pain. If there is a complete tear, surgical repair is indicated if the athlete desires to continue a pitching career.

Medial epicondylitis (golfer’s elbow) is another common cause of medial elbow pain in the individual with fused apophysis. It is commonly caused by overuse of the flexor pronator muscle groups at their origin at the medial humeral epicondyle. This occurs frequently in athletics or activities with repetitive wrist flexion. Tenderness is noted over the medial epicondyle and exacerbated by passive wrist extension or resisted wrist flexion. Treatment includes rest from the inciting activity, ice, stretching and strengthening of the wrist flexors, forearm straps, counterforce bracing, and analgesia. Ulnar nerve dysfunction can be a complication of valgus overload and can occur with any of the diagnoses previously discussed. Persisting paresthesia or motor weakness in the ulnar nerve distribution should be evaluated with electromyography and nerve conduction studies.

Lateral elbow pain can be caused by compression during the throwing motion at the radiocapitellar joint. Panner disease is osteochondrosis of the capitellum that occurs between ages 7 and 12 yr (Fig. 687-7). OCD of the capitellum occurs at age 13-16 yr (see Fig. 687-1). These 2 entities might represent a continuum of the same disease. Although patients with both conditions present with insidious onset of lateral elbow pain exacerbated by throwing, patients with OCD have mechanical symptoms (popping, locking) and, more commonly, decreased range of motion. Patients with Panner disease have no mechanical symptoms and often have normal range of motion. The prognosis of Panner disease is excellent, and treatments consist of relative rest (no throwing), brief immobilization, and repeat radiographs in 6-12 wk to assess bone remodeling. In OCD, radiographs show a more focal lesion in the capitellum with eventual flattening and potentially fragmentation. MRI scan can be very helpful in the diagnosis early on and with subsequent staging. A diagnosis of OCD requires orthopedic consultation with treatment dependent upon the severity of the lesion and fragmentation.

Lateral epicondylitis (tennis elbow), the most common overuse elbow injury in adults, is relatively uncommon in children and
adolescents. It is a tendinosis of the extensor muscle origin at the lateral humeral epicondyle commonly found in individuals performing activities requiring repetitive or prolonged grip. Tenderness is localized over the upper lateral epicondyle and is worsened with passive wrist flexion or resisted wrist extension. Treatment includes relative rest, analgesia, and specific stretching and strengthening exercises for the elbow and forearm. Improper equipment (i.e., wrong grip size or overstrung racket) and poor technique can contribute to onset of symptoms. Return to play should be gradual and progressive to prevent reinjury.

Elbow injuries can be minimized but not necessarily prevented by preseason stretching and strengthening exercises. The importance of core strengthening and scapular stabilization with respect to preventing elbow and shoulder injuries in the throwing athlete cannot be overstated. The most important consideration for preventing elbow injuries in throwers is limitation of the number of pitches and advising players, coaches, and athletes that they should stop immediately when they experience elbow pain. If it persists, they need medical evaluation. It has been recommended that a young pitcher have age specific limits on pitch counts including number of pitches thrown per game and per week, as well as maintaining appropriate days off between games pitched. A good rule of thumb is the maximal number of pitches per game should be approximately 6 times the pitcher's age in years.

Other less-common problems that cause elbow pain are ulnar neuropathy/subluxation, tricipital or bicipital tendonitis (distal), olecranon apophysisitis, and loose bodies. Non-sports-related injuries that need to be considered in the child with a painful elbow include congenital conditions, such as radial dysplasia, including radial ulnar synostosis and mild persistent brachial plexus palsy. The elbow is not an uncommon site for inflammatory arthritis, including juvenile idiopathic arthritis, sepsis, hemophilia, and sickle cell disease. Neoplasia to consider includes osteoblastomas and chondroblastomas, common in the diaphysis and epiphysis of longer bones, in addition to osteosarcoma. As always, in the child with persistent symptoms who is not responding to conservative care, further diagnostic work up is always indicated.

Bibliography is available at Expert Consult.

687.4  Low Back Injuries
Kevin P. Murphy and Aaron M. Karlin

SPONDYLOLYSIS, SPONDYLOLISTHESIS, AND FACET SYNDROME

Spondylolysis

Spondylolysis, a common cause of back pain in athletes, is a stress fracture of the pars interarticularis (see Chapter 679.6). It can occur at any vertebral level but is most likely at L4 or L5. Complete spondylolysis has never been found in the newborn. Its occurrence increases between the ages of 5.5 and 6.5 yr to a rate of 5%, close to the frequency of 5.8% in the white population. Prevalence in adolescent athletes evaluated for low back pain is 13-47%. Besides acute hyperextension that causes an acute fracture, the mechanism of injury is either a congenital defect or hypoplastic pars, which is exacerbated by lumbar extension loading, or a stress fracture caused by repetitive extension loading. Ballet, weightlifting, gymnastics, and football are examples of sports in which repetitive extension loading of the lumbar spine occurs; it occurs in any activity in which there is repetitive extension loading, including swimming.

Patients often present with pain of insidious onset. However, there may be a precipitating injury such as a fall or single episode of hyperextension. The pain is worse with extension, can radiate to the buttocks, and can eventually affect activities of daily living. Rest or supine positioning usually alleviates the pain.

On examination, the pain is reproduced with lumbar extension while standing, especially when standing on 1 leg (single-leg hyperextension test). Limited forward spinal flexion and tight hamstrings may be seen. Neurologic examination should be normal. There is well-localized tenderness to deep palpation just lateral to the spinous process on the affected side and is usually at L4 or L5.

The diagnosis is confirmed by finding a pars defect on an oblique lumbar spine radiograph. The defect is rarely seen on anteroposterior (AP) and lateral views. Bone single-photon emission CT is needed to confirm diagnosis if radiographs are normal. A plain CT scan can help to identify the degree of bony involvement and is sometimes used to assess healing.

Treatment includes pain relief and activity restriction. Rehabilitation consisting of trunk strengthening, hip flexor stretching, and hamstring stretching is important in most cases. A thoracic lumbar sacral orthotic on a temporary basis may be helpful for the spondylolytic stress fracture resistant to healing by alternative conservative means.

Spondylolisthesis and Facet Syndrome

Spondylolysis, spondylolisthesis, and facet syndrome are injuries posterior to vertebral elements. Spondylolisthesis occurs when bilateral pars defects exist and forward displacement or slippage of a vertebra occurs on the vertebra inferior to it (see Chapter 679.6). Facet syndrome has a similar history and physical examination findings as spondylolisthesis. It is caused by instability or injury to the facet joint, posterior to the pars interarticularis and at the interface of the inferior and spondylolytic articulating processes. Facet syndrome can be established by identifying facet abnormalities on CT or by exclusion, requiring a nondiagnostic radiograph and nuclear scan to rule out spondylolisthesis.

Treatment of posterior element injuries is conservative, directed at reducing the extension-loading activity, often for 2-3 mo. Body mechanics, posture principals, core strengthening, and lumbar pelvic stabilization routines can be very helpful in the functional recovery of the motivated athlete. Walking, swimming and cycling can be appropriate exercises also during the rehabilitation phase. Rarely spinal segmental fusion can be indicated in the athlete with spondylolisthesis and persistent symptomatic segmental instability despite further conservative care.

LUMBAR DISK HERNIATION, STRAIN, AND CONTUSION

Intervertebral disc injury in children and the young athlete is uncommon. In contrast to the selective motor and sensory deficits often observed in adults with disc herniation, athletes younger than 20 yr of age have pain or tenderness less commonly identified over the course of the sciatic nerve. Physical examination findings may be minimal but usually include pain with forward flexion and lateral bending. It is unusual to have a positive straight leg test or any neurologic deficit in the young athlete with an injured disc. There may be tenderness of the vertebral spinous process at the level of the disc. A general aching sensation in the lower back or upper buttocks may be present. MRI usually confirms a clinical diagnosis. Assuming the herniation is not large and the pain is not intractable, the treatment of choice is conservative with analgesia and physical therapy. Surgery is rarely necessary.

Acute lumbar strain or contusion can be seen in the younger athlete and is usually associated with precipitating activity often outside of the normal routine. Physical examination reveals tenderness in the paraspinal and lateral soft tissues often associated with recreating the mechanisms of injury. Thoracic and lumbar strain in the school-age child is associated with obesity, deconditioning, positive family history, and poorly supervised and equipped recreational activity. Up to 20% of youth have experienced back pain at some point in their life (younger than age 15 yr). The school-age backpack is rapidly becoming the most common cause of back pain of a benign nature in children. Up to 74% of school backpackers experience pain. Back pain is more common with the heavy backpack (greater than 10-20% of body weight), female gender, large body mass index, and single shoulder strap.

Treatment is conservative including analgesia, myofascial release, massage, and physical therapy, as tolerated. The natural history of acute
Bibliography
back pain in adults is that 50% are better in 1 wk, 80% in 1 mo, and 90% in 2 mo, regardless of therapy. The course of back pain in young athletes is likely similar given the elimination of obvious precipitating influence and/or activities, as discussed above.

**Sacroiliitis**

Sacroiliitis manifests as pain over the sacroiliac joints; it is usually chronic but occasionally associated with a history of trauma. Patients have a positive result with the **Patrick test**, which includes resting the foot of the affected side on the opposite knee (hip flexed 90 degrees), stabilizing the opposite iliac crest, and externally rotating the hip on the affected side (pushing the knee down and lateral). Symptomatic improvement with knee-to-chest maneuvers and subsequent posterior pelvic tilt may be present. A radiograph of the sacroiliac joints is indicated, and if results are positive, exploration for a rheumatologic disease (ankylosing spondylitis [see Chapter 156], juvenile rheumatoid arthritis [see Chapter 155], ulcerative colitis [see Chapter 336]) is warranted.

**Treatment** is with relative rest, nonsteroidal antiinflammatory drugs, and physical therapy. Ankylosing spondylitis is more likely if the onset of lower back pain is before age 40 yr, if there is morning stiffness that is associated with improvement with activity, and if the pain has a gradual onset and has lasted longer than 3 mo.

**OTHER CAUSES**

Non–sports-related causes of low back pain are numerous and include infection (osteomyelitis, diskitis) and neoplasia. These should be considered in patients with fever, weight loss, other constitutional signs, or lack of response to initial therapy. Osteomyelitis of the lower back or pelvis is often, but not always, associated with fever. Scheuermann disease needs to be considered more common in males and younger adolescents, and needs to be distinguished from symptomatic postural roundback and congenital decompensating kyphosis. Atypical Scheuermann disease or thoracolumbar apophysitis can progress and become the pediatric equivalent of an adult compression fracture. Benign tumors of the spine include osteoid osteoma with intense focal nighttime pain, not activity related and almost always relieved by aspirin or nonsteroidal antiinflammatory agents. Osteoblastoma, eosinophilic granuloma, aneurismal bone cyst, and fibrous dysplasia are additional benign tumors not to be excluded. Malignant tumors include neuroblastoma, spinal cord tumors, leukemia, and lymphoma. Wilms tumor can also manifest in childhood with insidious onset of limp and hip pain (see Chapter 678.3). Until the skeleton matures (Table 687-2), younger athletes are susceptible to apophyseal injuries (e.g., the anterior superior iliac spine). **Apophysitis** develops from overuse or from direct trauma. **Avulsion fractures** occur in adolescents playing sports requiring sudden, explosive bursts of speed (see Fig. 687-2). Large muscles contract and create force greater than the strength of the attachment of the muscle to the adjoining bone. The most common sites of avulsion fractures are the anterior superior iliac spine (sartorius and tensor fasciae lata), anterior inferior iliac spine (rectus femoris), lesser femoral trochanter (ilio-psoas), ischial tuberosity (hamstrings), and the iliac crest (abdominal muscles). Symptoms include localized pain and swelling, with decreased strength and range of motion. Bilateral radiographs are important in order to allow for comparison to assess for displacement, if any, of the fracture fragment. Significant displacement or presence of a large fragment may require orthopedic consultation. Initial **treatment** includes ice, analgesics, rest, and pain-free range-of-motion exercises. Crutches are usually needed for ambulation. Surgery is usually not indicated because most of these fractures—even large or displaced ones—heal well. Direct contact to the bone around the hip and pelvis causes exquisitely tender subperiosteal hematomas called.

**Table 687-2**

Age of Appearance and Fusion of Apophyses in Hip and Pelvis

<table>
<thead>
<tr>
<th>APOPHYSIS</th>
<th>APPEARANCE (YR)</th>
<th>FUSION (YR)</th>
<th>RELATED MUSCLE GROUP(S)</th>
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<td>16-18</td>
<td>Quadriceps</td>
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<tr>
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<td>13-15</td>
<td>21-25</td>
<td>Sartorius</td>
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<tr>
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<td>11-12</td>
<td>16-17</td>
<td>Iliopsoas</td>
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<td>Gluteal</td>
</tr>
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<td>Ischial tuberosity</td>
<td>13-15</td>
<td>20-25</td>
<td>Hamstrings</td>
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<tr>
<td>Iliac crest</td>
<td>13-15</td>
<td>21-25</td>
<td>Abdominal obliques Latissmus dorsi</td>
</tr>
</tbody>
</table>

AIIS, anterior inferior iliac spine; ASIS, anterior superior iliac spine.


**Bibliography** is available at Expert Consult.

**687.5 Hip and Pelvis Injuries**

Kevin P. Murphy and Aaron M. Karlin

Hip and pelvis injuries represent a small percentage of sports injuries, but they are potentially severe and require prompt diagnosis. Hip pathology can manifest as knee pain and normal findings on knee examination.

In children, **transient synovitis** is the most common cause. It usually manifests with acute onset of a limp, with the child refusing to use the affected leg and having painful range of motion on examination. There may be a history of minor trauma. This is a self-limiting condition that usually resolves in 48-72 hr.

**Legg-Calvé-Perthes disease** (avascular necrosis of the femoral head) also manifests in childhood with insidious onset of limp and hip pain (see Chapter 678.3). Until the skeleton matures (Table 687-2), younger athletes are susceptible to apophyseal injuries (e.g., the anterior superior iliac spine). **Apophysitis** develops from overuse or from direct trauma. **Avulsion fractures** occur in adolescents playing sports requiring sudden, explosive bursts of speed (see Fig. 687-2). Large muscles contract and create force greater than the strength of the attachment of the muscle to the apophysis. Biomechanical susceptibility of the pelvis allows separation to occur in the cartilaginous region between the apophysis and the adjoining bone. The most common sites of avulsion fractures are the anterior superior iliac spine (sartorius and tensor fasciae lata), anterior inferior iliac spine (rectus femoris), lesser femoral trochanter (ilio-psoas), ischial tuberosity (hamstrings), and the iliac crest (abdominal muscles). Symptoms include localized pain and swelling, with decreased strength and range of motion. Bilateral radiographs are important in order to allow for comparison to assess for displacement, if any, of the fracture fragment. Significant displacement or presence of a large fragment may require orthopedic consultation. Initial **treatment** includes ice, analgesics, rest, and pain-free range-of-motion exercises. Crutches are usually needed for ambulation. Surgery is usually not indicated because most of these fractures—even large or displaced ones—heal well. Direct contact to the bone around the hip and pelvis causes exquisitely tender subperiosteal hematomas called.
Bibliography
hip pointers. These injuries are more commonly seen around the ante-
rior superior iliac spine and the iliac crest. Limited active range of 
motion can be identified about the hip brought on by contracture of 
locally attached musculature such as hip flexors and hip abductors. 
Symptomatic care includes rest, ice, analgesia, and protection from 
reinjury.

Slipped capital femoral epiphysis usually occurs in the 11-15 yr age 
range during the time of rapid linear bone growth (see Chapter 678.4).
A femoral neck stress fracture can manifest as vague progressive hip 
ain in an endurance athlete. Girls with the female athlete triad are 
especially at risk. This diagnosis should always be kept in mind in the 
running athlete with vague anterior thigh pain. On examination, there 
may be pain with passive stretch of the hip flexors and pain with hip 
rotation. If radiographs do not demonstrate a periosteal reaction con-
sistent with a stress fracture, a bone scan or MRI may be required.
Orthopedic consultation is necessary in femoral neck stress fractures 
because of their predisposition to nonunion and displacement with 
minor trauma or continued weight bearing. These fractures carry 
increased risk of avascular necrosis of the femoral head.

Osteitis pubis is an inflammation at the pubic symphysis that may be 
caused by excessive side-to-side rocking of the pelvis. It can be seen in 
an athlete in any running sport and is more common in sports requir-
ning more use of the adductor muscles such as ice hockey, soccer, and 
inline skating. Athletes typically present with vague groin pain that 
may be unilateral or bilateral. On physical examination, there is tender-
ness over the symphysis and sometimes over the proximal adductors.
Adduction strength testing causes discomfort. Radiographic evidence 
(irregularity, sclerosis, widening of the pubic symphysis with osteoly-
sis) might not be present until symptoms are present for 6-8 wk; a bone 
scan and MRI are more sensitive to early changes. Relative rest for 
6-12 wk may be required. Some patients require corticosteroid injec-
tion as adjunctive therapy.

Acetabular labrum tears can occur in the hip, similar to glenoid 
labrum tears in the shoulder. Athletes might have a history of trauma 
and complain of sharp anterior hip pain associated with a clicking or 
catching sensation. Clinical diagnosis is difficult; magnetic resonance 
arthrography is useful for diagnosis.

Snapping hip syndrome is caused by the iliopsoas musculotendinous 
unit riding over the pectineal eminence of the pelvis, anterior hip 
capsule or the iliobtubal band over the greater trochanter. Lack of flex-
ibility in these muscles results in snapping, as the musculotendinous 
unit slides over the associated bony prominences. It is commonly seen 
in ballet dancers and runners; it can occur as an acute or overuse injury 
(more common). Athletes present with either a painful or painless click 
or snap in the hip, usually located lateral or anterior and deep in the 
joint. Examination often reproduces the symptoms. Radiographs are 
not usually needed in the work-up. Core weakness may be present leading to excessive movement about the hip girdle contributing to 
increased sliding of the tight muscle over the boney prominence.

Treatment involves an analgesia, relative rest, biomechanical assess-
ment, core flexibility, with stretching and strengthening of the involved 
soft tissue. The athlete may return to activity as tolerated. Common 
soft-tissue injuries around the hip and pelvis include strain and tendi-
nosis of the hip flexors (groin) and hamstrings in addition to quadri-
ceps contusions and greater trochanteric bursitis. Sports hernia also 
needs to be considered in the athlete with insidious onset exer-
tional groin pain, worsening with Valsalva. Pain may radiate into the 
anterior thigh, inguinal region, rectum, perineum and/or scrotum.
Tenderness to deep palpation may or may not be present. Resisted hip 
flexion and/or half sit ups may be provocative. MRI, CT scan, and bone 
scan can be helpful in ruling out other diagnoses, but usually are nega-
tive with respect to sports hernia pathology. Patients who continue 
with symptoms despite conservative care may be surgical candidates.
Surgical repair can be 95% successful if anatomical lesions are identi-
ified. As with any child or adolescent presenting with a painful hip or 
pelvis, non–sports-related conditions need to be considered. Different-
tial diagnoses may also include the epiphyseal dysplasias, recurrent or 
undiagnosed congenital or developmental hip dysplasia, additional 
causes of avascular necrosis including sickle cell anemia, Gaucher 
disease, rheumatoid arthritis, and other collagen disorders including 
steroid therapy. Traumatic hip dislocations are relatively rare in chil-
dren but not to be overlooked. Leg-length discrepancies can be symp-
tomatic at the hip in an otherwise able bodied child. Common tumors 
in lower extremities include osteosarcoma along with osteoblastoma, 
aeurysmal bone cysts, and fibrous dysplasia (more common in the 
pelvis). Metastatic tumors to the lower extremities include neuroblas-
toma and lymphomas of various types, not to exclude leukemic infiltra-
tion with joint arthralgia. Child abuse always needs to be considered 
in a young patient with musculoskeletal pain no matter what the socio-
economic status.

Bibliography is available at Expert Consult.

687.6 Knee Injuries

Kevin P. Murphy and Aaron M. Karlin

Knee pain is common among adolescents. Acute knee injuries that 
cause immediate disability are likely to be due to fracture, patellar 
dislocation, anterior cruciate ligament (ACL) injury, or meniscal tear.
The mechanism of injury is usually a weightbearing event. If the knee 
swells more immediately (within several hours of injury), the swelling 
is likely caused by a hemarthrosis and more severe injury. The injury 
most likely to occur with a hemarthrosis is an ACL injury. This injury 
(rare in children younger than 12 yr) is usually caused from being hit 
directly, landing off-balance from a jump, quickly changing direction 
while running, or hyperextension. Instability is often present but may 
be hard to detect in the presence of significant swelling. Girls are more 
than twice as likely as boys to disrupt their ACL, with a soccer injury 
a common scenario. Often, these injuries are associated with an avuls-
ion injury of the anterior tibial spine. The majority of athletes with 
significant ACL injury need orthopedic consultation with consider-
ation of ACL reconstruction. Chronic ACL insufficiency may increase 
the risk of meniscal injury and further joint dysfunction. Additional 
physial-sparing reconstructions with minimal risk of growth arrest or 
angular deformity have been reported with success in children younger 
than 12 yr and adolescents.

Posterior cruciate ligament injury occurs from a direct blow to the 
region of the proximal tibia, such as might occur with a dashboard 
damage or a fall to the knees in volleyball. Posterior cruciate ligament 
injuries are rare and are usually treated nonsurgically.

Medial collateral ligament injuries result from a varus blow to the 
outside of the knee. Isolated lateral collateral ligament injuries are 
uncommon and result from significant varus knee stress. Because they 
are extratendinous, lateral collateral ligament injuries should not produce 
much of a knee effusion and are generally less disabling. Isolated 
medial and lateral collateral injuries are generally managed nonsurgi-
cally with conservative care and appropriate rehabilitation.

Meniscal tears generally occur by the same mechanisms as ACL 
injuries. They are often associated with less hemarthrosis, significant 
joint line pain, and increased pain with full knee flexion. MRI scan 
will often yield the diagnosis; conservative care, including PRICE 
principles, is therapeutic for smaller injuries. Orthopedic consultation 
is indicated for larger tears not healing with conservative care and 
classifying significant dysfunction inhibiting quality of life. An isolated 
meniscal tear in a child younger than age 10 yr is unusual, with surgery, 
again, only if conservative measures fail. The choice is often repair of 
the meniscus rather than surgical resection because of the increased 
potential in children for cartilaginous healing. Physical injuries tend 
to predominate in younger patients, whereas the more skeletally 
mature adolescents tend to sustain medial collateral ligament injuries. 
Discoid meniscus (anatomical variant covering lateral tibial plateau) 
always needs to be considered, particularly in children younger than 
age 12 yr.

Patellar dislocation occurs most often as a noncontact injury when 
the quadriceps muscles forcefully contract to extend the knee while the 
lower leg is externally rotated. Patellar dislocation is the second most
Bibliography
common cause of hemarthrosis. The patella is almost always dislocated laterally, and this motion tears the medial patellar retinaculum, causing bleeding in the joint. Recurrent episodes of patellar instability are associated with less swelling. Patellar dislocations are often associated with genu valgum, external tibial torsion, and general ligamentum hyperlaxity. Exercises to strengthen the quadriceps, particularly the vastus medialis, and the use of patella-tracking braces may be helpful. Recurrent instability can require surgical intervention. Surgical stabilization of the medial patellar tissues and lateral retinacular release can be helpful in more difficult cases.

**INITIAL TREATMENT OF ACUTE KNEE INJURIES**

The physician should inspect for an effusion and obvious deformities; if any deformity is present, the physician should assess neurovascular status and transfer the patient for emergency care as indicated. If no gross deformities are present and neurovascular integrity is intact, initial maneuvers include full passive extension and gentle valgus and varus stress to the knee while in extension. Comparison to the non-injured knee is always helpful for assessing degrees of laxity and range of motion. The patient’s ability to contract the quadriceps should be noted. Pain occurring with quadriceps contraction or inability to contract the quadriceps muscle implies an injury to the extensor mechanism. Tenderness over the medial patella, medial retinaculum, or above the adductor tubercle is associated with a patellar dislocation (usually lateral). Point tenderness is consistent with fracture or injury to the underlying structure. Meniscal tears usually manifest as tenderness along the joint line, accentuated with flexion of the knee often beyond 90 degrees. Pain or limitation in either flexion or extension while rotating the tibia implies a meniscal injury. Ligament injury is manifested as pain or laxity with the appropriate maneuver (Fig. 687-8). If a patient cannot weight-bear pain free or has clinical signs of instability, significant swelling or other major concern, the knee should be immobilized, crutches provided, and plain radiographs obtained. If the patella is dislocated, reduction may be achieved with gentle active assistive knee extension. Straight-leg immobilizers offer no structural support and are only used for comfort and reminding the patient to be careful with any weight-bearing. A derotational hinge brace may be indicated for stabilization such as an injury when both ACL and medial collateral ligament have been traumatized. The leg should be elevated and an elastic wrap can be applied for compression (PRICE principles).

**CHRONIC INJURIES**

**Patellofemoral Stress Syndrome**

Patellofemoral stress syndrome (PFSS) is the most common cause of anterior knee pain. PFSS is also known as *patellofemoral pain syndrome* or *patellofemoral dysfunction* (see Chapter 677.5). It is a diagnosis of exclusion used to describe anterior knee pain that has no other identifiable pathology. Chondromalacia may be seen in association with softening of the articular cartilage underneath the patellar surface. Pain is usually difficult to localize. Patients indicate a diffuse area over the anterior knee as the source, or they might feel as if the pain is coming from behind the patella. Bilateral pain is common, and pain is often worse going up stairs, after sitting for prolonged periods, or after squatting or running. There should be a negative history for significant swelling, which would indicate a more serious injury. History of change
in activity is common, such as altered training surface or terrain, increased training regimen, or performance of new tasks.

Examination should include evaluation of stance and gait for lower limb alignment, musculature, and midfoot hyperpronation. Flexibility of the hamstrings, iliobibial band (ITB), and gastrocnemius should be assessed, because stress is increased across the patellofemoral joint when these structures are tight. Hip range of motion should be assessed to rule out hip pathology. Medial patellar tenderness or pain with compression of the patellofemoral joint confirms the diagnosis in the absence of a significant effusion and other positive findings. PFSS is a clinical diagnosis usually managed without imaging.

**Treatment** focuses on assessing and improving flexibility, strength, and gait abnormalities. In the presence of midfoot hyperpronation (ankle valgus), new shoes or use of arch supports can improve patellofemoral mechanics and improve pain. Ice and an analgesic can be used to help control pain. Reduced overall activity or training is important initially in rehabilitation along with limiting knee flexion no greater than 60 degrees as possible. Short arc quadriceps strengthening exercises can be helpful (active knee extension with or without resistance between 0 and 30 degrees of knee flexion). Therapeutic taping techniques to help improve patella tracking within the trochlear groove can be helpful with the assistance of a sports physical therapist.

**Osgood-Schlatter Disease**

**Osgood-Schlatter disease** is a traction apophysitis occurring at the insertion of the patellar tendon on the tibial tuberosity (see Chapter 677.4). Because it is also related to overuse of the extensor mechanism, Osgood-Schlatter disease is treated like PFSS. A protective pad to protect the tibial tubercle from direct trauma can be used. Therapeutic taping of the tibial tubercle may provide comfort, along with well-fitted knee sleeves and/or straps. Nonsteroidal antiinflammatory drugs are often prescribed as well. Pain-free strengthening of weightbearing soft tissues using more closed-kinetic chain techniques may be best. PRICE principles apply. Make certain that patients and parents are aware that resolution is usually slow, often requiring 12-18 mo. Complications are rare and can include growth arrest with recurvatum deformity and rupture or avulsion of the patellar tendon/tibial tubercle.

**Other Chronic Injuries**

**Sinding-Larsen-Johansson disease** is a traction apophysitis occurring at the inferior pole of the patella. It occurs most often in volleyball and basketball athletes. **Treatment** is similar to that of PFSS and Osgood-Schlatter disease.

Patellar tendinosis (jumper’s knee) is caused by repetitive microtrauma of the patellar tendon, usually at the inferior pole of the patella. In approximately 10% of the cases, the quadriiceps tendon above the patella is affected. It is associated with jumping sports but occurs in runners as well. **Treatment** is similar to that for PFSS. Relative rest is more important in patellar tendinosis because chronic pain can be associated with irreversible changes in the tendon.

**ITB friction syndrome** is the most common cause of chronic lateral knee pain. Generally it is not associated with swelling or instability. It is from friction of the ITB along the lateral knee, resulting in bursitis. Tenderness is elicited along the ITB as it courses over the lateral femoral condyle or at its insertion at the Gerdy tubercle, along the lateral tibial plateau. Tightness of the ITB is also noted using the Ober test. To perform an Ober test, the athlete lies on one side and the superior hip is extended with the knee flexed. The examiner holds the ankle in midair, and if the knee moves inferiorly, it implies a flexible ITB and a negative Ober test. If the knee and leg stay in midair, the ITB is tight and the Ober test is positive. **Treatment** principles follow those for PFSS, except emphasis is on improving flexibility of the ITB.

Other soft-tissue injuries not to be excluded include prepatellar and pes anserine bursitis, pical syndromes, and Hoffa syndrome. The pes anserine bursa lies just under the conjoined tendon of the sartorius, gracilis, and semitendinous muscles as it attaches medially to the proximal tibia. In Hoffa syndrome, the fat pad beneath the patella and posterior to the patella ligament becomes pinched with anterior pain on knee extension. These conditions are generally more common in adolescents, those with genu recurvatum, and long distance runners. Non–sports-related conditions, again, always need to be considered in the context of any child with a painful knee, particularly in a child younger than age 12 yr. These include conditions such as OCD (see Chapter 677.3), which is most common on the lateral aspect of the medial femoral condyle. Inflammatory and infectious arthritis, Baker’s cyst (see Chapter 677.2), and hip pain referred to the knee are additional considerations. Tumors more common to the knee joint include osteogenic sarcoma (distal femoral and proximal tibial), histiocytosis X in the diaphysis, and eosinophilic granuloma in the epiphysis of long bones. Metastatic tumors to the lower extremities include neuroblastoma and lymphomas of various types. As with any apparent musculoskeletal injury in a child not responding to conservative care, more in-depth diagnostic pursuit for alternative pathology is mandatory.

**Bibliography** is available at Expert Consult.

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**687.7 Lower Leg Pain: Shin Splints, Stress Fractures, and Chronic Compartment Syndrome**

**Kevin P. Murphy and Aaron M. Karlin**

Stress injury to the bones of the lower leg occurs on a continuum from mild injury (shin splints) to stress fracture. All occur by an overuse mechanism.

**Shin splints**, also known as medial tibial stress syndrome, manifests with pain along the medial tibia or both tibiae and is the most common overuse injury of the lower leg. The pain initially appears toward the end of exercise, and if exercise continues without rehabilitation, the pain worsens and occurs earlier in the exercise period. There is diffuse tenderness over the lower third to half of the distal medial tibia. Any focal tenderness or tenderness of the proximal tibia is suspicious for a stress fracture. A stress fracture tends to be painful during the entire workout. Shin splints can usually be distinguished from a **tibial stress fracture** in which the tenderness is more focal (2-5 cm) and more severe. Shin splints and stress fracture represent a continuum of stress injury to the tibia and are thought to be related to traction of the soleus on the tibia. Eccentric contraction of the medial aspect of the soleus is required to control pronation from initial contact to mid-stance with running. This contraction increases the stress of the fascial origin of the soleus possibly through Sharpey’s fibers causing disruption to the tibial periosteum and fibrocartilaginous attachments.

The diagnosis can be made by history and physical examination. Findings on plain radiographs of the tibia are normal with shin splints and in tibial stress fractures within the 1st 2 wk of the injury. Afterward, the radiographs can demonstrate periostal reaction if a stress fracture is present. Sensitivity of plain radiographs may be increased by obtaining 4 views of the tibia: AP, lateral, and both oblique views. A bone scan is the most sensitive test to diagnose stress fractures; it demonstrates discrete tracer uptake at the site(s) of the stress fracture. Increased uptake may be noted in the presence of shin splints, but in a fusiform pattern along the periosteal surface. If results of the bone scan are normal, the diagnosis is likely to be shin splints or chronic compartment syndrome. MRI has replaced bone scan as the most sensitive tool for diagnosing stress fractures in long bones in many medical centers.

The treatment of shin splints and tibial stress fractures is similar, involving relative rest, correcting training errors and addressing quartile muscle imbalances and abnormal mechanical alignment. Orthotics and/or new shoes may be useful in patients who hyperpronate. Fitness can be maintained with non-weightbearing activities, such as swimming, cycling, and water jogging. With shin splints, after...
Bibliography

7-10 days, patients can usually start on the walk-jog program. If pain worsens, 2-3 pain-free days are required before resuming the walk-jog program. Ice should be used daily and an analgesic should be used for pain control. Stretching the plantar flexors, hamstrings and strengthening the ankle dorsiflexors may be useful. Therapeutic taping and wrapping techniques to support the soft-tissue attachments have been useful in some when directed by a skilled sports therapist. Being pain free for 7-10 days is recommended before exercises are commenced. Individuals with pain at rest and not responsive to treatment require continued suspicion for stress fracture.

**Chronic compartment syndrome** occurs in an athlete in a running sport, usually during a period of heavy training. It is caused by muscle hypertrophy and increased intracompartmental pressure with exercise. There is typically a pain-free period of about 10 min at the beginning of a workout before onset of constant throbbing pain that is difficult to localize. It lasts for minutes to hours after exercise and is relieved by ice and elevation. In a classic case, there is numbness of the foot associated with high pressure within the corresponding muscle compartment. The most common compartment affected is the anterolateral compartment with compression of the fibular nerve followed by the deep posterior compartment. The physical examination in the office is often normal but weakness of the extensor hallucis longus (anterolateral compartment) and decreased sensation between the 1st and 2nd toe may be present. X-rays, bone scan, and MRI are negative and are used to rule out other conditions. Compartment pressure measurements are the test of choice. Treatment involves reduction of activity, antiinflammatory medication, orthotics (hyperpronation), heel cord stretching, light strengthening of distal muscle, optimal footwear, and cross-training (swimming, cycling and water jogging). Cryotherapy and superficial heat can be of help in addition. Persistent systems, despite conservative care, require fasciotomy (successful in up to 90% of cases).

**Bibliography is available at Expert Consult.**

### 687.8 Ankle Injuries

*Kevin P. Murphy and Aaron M. Karlin*

Ankle injuries are the most common acute athletic injury. Approximately 85% of ankle injuries are sprains, and 85% of those are inversion injuries (foot planted with the lateral fibula moving toward the ground), 5% are eversion injuries (foot planted with the medial malleolus moving toward the ground), and 10% are combined.

#### EXAMINATION AND INJURY GRADING SCALE

In obvious cases of fracture or dislocation, evaluating neurovascular status with as little movement as possible is the priority. If no deformity is obvious, the next step is inspection for edema, ecchymosis, and anatomic variants. Key sites to palpate for tenderness are the entire length of the fibula; the medial and lateral malleoli; the base of the 5th metatarsal; the anterior, medial, and lateral joint lines; and the navicular and the Achilles tendon complex. Assessment of active range of motion (patient alone) in dorsiflexion, plantar flexion, inversion, and eversion along with gentle resisted range of motion can be helpful.

Provocative testing attempts to evaluate the integrity of the ligaments. In a patient with a markedly swollen, painful ankle, provocative testing is difficult because of muscle spasm and involuntary guarding. It is more useful on the field before much bleeding and edema have occurred. The anterior drawer test assesses for anterior translation of the talus and competence of the anterior talofibular ligament. The inversion stress test examines the competence of the anterior talofibular and calcaneofibular ligaments (Fig. 687-9). In the acute setting, the integrity of the tibiobular ligaments and syndesmosis is examined by the syndesmotic squeeze test. Pain with squeezing the lower leg implies injury to the interosseous membrane and syndesmosis between the tibia and fibula, making a high ankle sprain or more severe injury suspicious. Athletes with this injury cannot bear any weight and also have severe pain with external rotation of the foot. Occasionally, the peroneal tendon dislocates from the fibular groove simultaneously with an ankle sprain. To assess for peroneal tendon instability, the examiner applies pressure from behind the peroneal tendon with resisting eversion and plantar flexion, and the tendon pops anteriorly. If either a significant syndesmotic injury or an acute peroneal dislocation is suspected, orthopedic consultation should be sought.

#### RADIOGRAPHS

AP, lateral, and mortise views of the ankle are obtained when patients have pain in the area of the malleoli, are unable to bear weight, or have focal bone tenderness over the distal tibia or fibula. The Ottawa ankle rules help define who requires radiographs (Fig. 687-10). A foot series (AP, lateral, and oblique views) should be obtained when patients have pain in the area of the midfoot or bone tenderness over the navicular or 5th metatarsal. It is important to differentiate an avulsion fracture of the proximal 5th metatarsal (Dancer’s fracture) from the Jones fracture of the proximal 5th metatarsal (a lucency about 2 cm from the proximal end). The former is treated more like an ankle sprain; the latter fracture has an increased risk of nonunion and requires orthopedic consultation. Injury to the deltoid ligament in the medial ankle (more rare) should raise the question of proximal fibular fracture. In this circumstance more proximal tibial imaging may be necessary. The talar dome fracture is manifested as an ankle sprain that does not improve. Radiographs on initial presentation can have subtle abnormalities. Any suspicion on the initial radiographs of a talar dome fracture warrants orthopedic consultation and further imaging. In the early adolescent, always look carefully at the tibial epiphysis. Nondisplaced Salter III fractures can be subtle and need to be recognized early and referred to an orthopedic surgeon promptly.

#### INITIAL TREATMENT OF ANKLE SPRAINS

Ankle sprains need to be treated with PRICE. This should be followed for the 1st 48-72 hr after the injury to minimize bleeding and edema. For an ankle injury, this might consist of crutches and an elastic wrap, although other compression devices such as an air stirrup splint work quite well. This allows early weight-bearing with protection and can be removed for rehabilitation. It is important to start a rehabilitation program as soon as possible.

#### Rehabilitation

Rehabilitation should begin the day of injury; for patients who have pain with movement, isometric strengthening can be started. Early phase intervention includes restoration of functional range of motion, strengthening with emphasis on peroneal musculature and early sensory proprioceptive training. Later intervention includes
Bibliography

higher-level balance activities, advanced proprioception exercises, and endurance training. When determining when an athlete is ready for running, there must be full range of motion and nearly full strength compared to the uninjured side. While standing on the uninjured side only, the athlete is instructed to hop 8-10 times, if possible. When this can be achieved without pain on the injured side, the athlete can begin to run, starting out with jogging and gradually progressing in speed, and finally to sprints. The athlete must stop if there is significant pain or limp. Finally, before returning to sport, the athlete must be able to sprint and change directions off the injured ankle comfortably. Performing some sport-related tasks is also helpful in determining readiness for return to play.

Recurrent ankle injuries are more likely in patients who have not undergone complete rehabilitation. Ankle sprains are less likely in players wearing high-top shoes. Proper taping of the ankle with adhesive tape can provide functional support but loosens with use and is often unavailable. Lace-up ankle supports are felt to be more useful for preventing recurrences by many. They are more supportive than tape and can be tightened repeatedly during the course of a practice or a game. Most sports physicians recommend their use indefinitely to help prevent further sprains. Surgery is a consideration for chronic mechanical instability with lateral complex ligamentous laxity in the failure of more conservative care. Salter-Harris grade I distal fibular fractures need careful consideration, particularly in the child younger than 12 yr old. The physeal plates are generally the weakest link in the musculoskeletal chain and tend to slide or pull apart before the surrounding soft tissue and/or ligaments tear in this younger population. Toddler’s fracture also needs to be considered especially in those younger than age 8 yr. The proposed mechanism involves shear stress with lack of displacement because of the periosteam that is relatively strong compared to the elastic bone in younger children. Additional radiographs may be inconspicuous (a faint spiral oblique line) or even normal. After 1 or 2 wk callous develops. The condition can be mistaken for osteomyelitis, transient synovitis, and/or even child abuse. Toddler’s fracture usually occurs in the lower third of the tibia, whereas nonaccidental injury typically affects the upper two-thirds or midshaft of the tibia. Other, more rare conditions that cannot be excluded include os fibulare, a congenital unfused secondary ossification center of the distal fibula. This can be seen in younger patients with recurrent ankle sprains, particularly as their body weight and activity increase during the early academic years. Tarsal coalitions can be seen also in the presence of ankle sprains in younger children the most common being talocalcaneal and calcaneal navicular. More common muscular strains and/or tendinosis remains more prevalent in the older child and adolescent including peroneal, posterior tibialis, and gastrocnemius/Achilles types. Tarsal tunnel syndrome is also more prevalent in the adolescent/younger adult and can be associated with medial ankle pain with burning or tingling into the sole of the foot.

**Bibliography is available at Expert Consult.**

### 687.9 Foot Injuries

**Kevin P. Murphy and Aaron M. Karlin**

**Metatarsal stress fractures** can occur in any running athlete. The history is insidious pain with activity that is getting worse. Examination reveals point tenderness over the midshaft of the metatarsal, most commonly the 2nd or 3rd metatarsal. Radiographs might not show the periosteal reaction before pain has been present for 2 wk or more. **Treatment** is relative rest for 6-8 wk. Shoes with good arch supports reduce stress to the metatarsals.

Vague dorsal foot pain in an athlete in a running sport can represent a navicular stress fracture. Unlike other stress fractures, it might not localize well on examination. If there is any tenderness around the navicular, a stress fracture should be suspected. This stress fracture can take many weeks to show up on plain radiographs, so a bone scan or MRI should be obtained to make the diagnosis. Because this fracture is at high risk of nonunion, immobilization and non-weightbearing for 8 wk is the usual treatment. A CT scan should be obtained to document full healing after the period of immobilization.

**Sever disease** (calcaneal apophysitis) occurs at the insertion of the Achilles tendon on the calcaneus and manifests as activity-related pain (see Fig. 687-3). It is more common in boys (2:1), is often bilateral, and usually occurs between ages 8 and 13 yr. Tenderness is elicited at the insertion of the Achilles tendon into the calcaneus, especially with squeezing the heel (positive squeeze test). Sever disease is associated with tight Achilles tendons and midfoot hyperpronation that puts more stress on the plantar flexors of the foot. **Treatment** includes relative rest, ice, massage, stretching, and strengthening the Achilles tendon. Correcting the midfoot hyperpronation with orthotics, arch supports, or better shoes is important in most athletes with Sever disease. If the foot is neutral or there is mild hyperpronation, in-heel
Bibliography


lifts can be helpful to unload the Achilles tendon and its insertion. With optimal management, symptoms improve in 4-8 wk. Generally, if there is no limp during the athletic activity, young athletes with Sever disease should be allowed to play.

**Plantar fascitis** is an overuse injury resulting in degeneration of the plantar aponeurosis. Rare in prepubertal children, this diagnosis is more likely in an adolescent or young adult. Athletes report heel pain with activity that is worse with first steps of the day or after several hours of non-weightbearing. Tenderness is elicited on the medial calcaneal tuberosity. Relative rest from weightbearing activity is helpful. Athletes get plantar fasciitis when shoes are worn with inadequate arch supports. New shoes or use of semirigid arch supports often lessen the pain. Stretching the calves and plantar fascia helps, assisted at times with therapeutic ultrasound treatment. Some patients benefit from night splints even though they can make sleep difficult. As long as there is no limping with athletic activity, the athlete may continue participation. Complete recovery is usually seen at 6 mo. Corticosteroid and extracorporeal shock-wave therapy are reserved for severe, chronic cases.

**Calcaneal stress fracture** is seen in the older adolescent or young adult involved in a running sport. There is heel pain with any weight-bearing activity. The physical examination reveals pain with squeezing the calcaneus. Sclerosis can show up on the AP and lateral radiographs after 2-3 wk of pain. A bone scan or MRI needs to be performed to clinch the diagnosis in some cases. The calcaneus is an uncommon location for a stress fracture; it is associated with osteopenia (amenorrheic girls). **Treatment** is rest from running and other weight-bearing activity for at least 8 wk. Immobilization is rarely necessary.

**Flatfeet or pes planus** may be flexible or rigid. Flexible pes planus is usually asymptomatic, at least in the early years and is the most common type found in children. Scaphoid pads or medial inserts may be helpful to create plantigrade weightbearing posture. Untreated sports progression may occur with compensatory hallux valgus, planovalgus, and secondary bunion and toe deformities. With progression pain may develop, along with shortening in the peroneal musculature. Rigid pes planus is a congenital deformity associated with other anomalies in 50% of cases. It is caused by failure of the tarsal bones to separate leaving a bony cartilaginous or fibrous bridge or coalition between 2 or more tarsal bones. Talocalcaneal coalitions are more symptomatic between 8 and 12 yr of age, whereas calcaneal navicular coalitions are more symptomatic between 12 and 16 yr of age. Symptoms are insidious with occasional acute arch, ankle, and midfoot pain, at times brought on with sports-related activities. The hindfoot often does not align in its normal varus position on tiptoe maneuvers. Patients are predisposed to ankle sprains secondary to limited subtalar motion and stress to the subtalar and transverse tarsal joints frequently causes pain. CT scans are diagnostic and initial treatment is conservative with short leg casting and/or molded orthoses and rest. In the case of failure of conservative care, surgical intervention is usually necessary. Rigid cavus feet can also be associated with metatarsalgia, clawing, and intrinsic muscle atrophy, all possible in the young athlete. With a cavus foot, underlying neurologic conditions, such as Charcot-Marie-Tooth disease, spinal dysraphism, Friedrich ataxia, or other spinal tumor, need be considered. Custom-molded orthotics may be helpful. Family history can be critical. Coleman block test can help determine hindfoot flexibility and more rigid vs flexible pes planus. Plantar fascial surgical release is standard for all cavus foot procedures. Accessory navicular bones and sesamoiditis need to be considered in all symptomatic feet, especially those with rigid components. These conditions are more common in the adolescent or younger adult and can be exacerbated with sporting activities.

Other conditions not to be excluded include Lisfranc sprain and/or dislocation, more common in football linemen or other athletes requiring heavy loading on the mid and forefoot joints and gymnasts using the balance beam. Lisfranc joint is the tarsal metatarsal articulation of the 3 cuneiform bones and the cuboid with the 5 proximal metatarsals. Turf toe can be seen, particularly in the older child and/or adolescent running on artificial or synthetic surfaces. It usually involves hyperextension through the 1st metatarsal phalangeal joint, spraining the ligaments surrounding the joint often in a football and/or soccer activity.

Iselin apophysitis is an apophysitis that occurs at the tuberosity of the fifth metatarsal. The apophysitis at this site appears between the ages of 9 and 14 yr and is located within the insertion of the peroneus brevis tendon. This condition can be a predisposing factor to the Dancer’s fracture (see Chapter 687.8). Osteochondroses (see Chapter 674.08) of the foot to always consider include Freiberg disease, which involves collapse of the articular service and subchondral bone, usually of the 2nd metatarsal. Kohler disease involves irregular ossification of the tarsal navicular joint with localized pain and increased density. Freiberg disease is more common in girls between the ages of 12 and 15 yr, whereas Kohler disease occurs in younger individuals, age 2-9 yr, and is frequently reversible with conservative care including orthoses and casting.

Bibliography is available at Expert Consult.
Bibliography


Concussion is defined as a traumatically induced transient disturbance of brain function that involves a complex pathophysiologic process. Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an “impulsive” force transmitted to the head, whether these are linear or rotational forces. Concussion is a subset of mild traumatic brain injury; it is important to communicate this fact to families and patients as the word “concussion” unintentionally and incorrectly has been found to communicate to some families that a brain injury has not occurred, resulting in less-than-adequate follow-up.

EPIDEMIOLOGY
At least 1.6-3.8 million concussions occur in the United States each year during competitive sports and other recreational activities. This number is likely to represent only a fraction of the true incidence as there is underreporting of symptoms by athletes from direct withholding of information to continue participation and poor understanding of their symptoms. From 1997 to 2007, visits to emergency departments for sports concussion doubled in the 8-13 yr old group; in 14-19 yr olds, the incidence has increased by more than 200%. Activities include football, bicycling, hockey, lacrosse, soccer, field hockey, basketball, and playground injuries.

PATHOPHYSIOLOGY
The pathophysiologic process following a concussion is best described as an “energy crisis” following a neurometabolic cascade. In animal models, these ionic and metabolic events, along with microscopic axonal injury, results in a desperation use of glucose to begin the healing process. The increased energy demand is met with a decreased cerebral blood flow, resulting in less available energy for other brain processes and a true mismatch of energy supply and demand.
ASSESSMENT OF THE INJURED PLAYER

The most current assessment tools are the Sport Concussion Assessment Tool (SCAT3) and the Child-SCAT3 for children ages 5-12, available at: http://bjsm.bmj.com/content/47/5/259.citation; http://bjsm.bmj.com/content/47/5/263.citation

These tests include the Glasgow coma scale, presence and duration of loss of consciousness, memory of the activity ("Who scored last?" "What team did you play last week?"); general memory/orientation (date, day of week, season), short-term memory (list 3 words and have patient repeat), concentration (give digits: 5-8-3, and have patient repeat backwards or do serial 7s), balance testing (double, single, tandem leg stances), finger to nose coordination, and cognitive testing (repeat list of words).

The signs and symptoms of concussion fall into 4 categories: physical, cognitive, emotional, and sleep (Table 688-1), with the most common symptom reported being headache. Transient loss of consciousness occurs in less than 10% of concussions and does not correlate with severity of injury. Assessment can be challenging as several or only 1 of the symptoms listed are identified. Furthermore, patients with preexisting mental health disorders such as depression or attention-deficit/hyperactivity disorder may experience exacerbations in their symptoms, making them more difficult to control.

Table 688-1 Postconcussion Symptom Scale

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
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<tbody>
<tr>
<td>Headache</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Balance problems</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Trouble falling to sleep</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Excessive sleep</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Loss of sleep</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Light sensitivity</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Noise sensitivity</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Irritability</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Sadness</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>More emotional</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Numbness</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Feeling “slow”</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Feeling “foggy”</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Difficulty remembering</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>Visual problems</td>
<td>0 1 2 3 4 5 6</td>
</tr>
</tbody>
</table>

Scale: 0, no symptoms; 3, moderate; 6, severe.

Use of the postconcussion symptom scale. The athlete should complete the form, on the athlete’s own, by circling a subjective value for each symptom. This form can be used with each encounter to track progress toward symptom resolution. Many athletes may have some of these reported symptoms at a baseline, such as concentration difficulties in the patient with attention-deficit or sadness in an athlete with underlying depression. This must be taken into consideration when interpreting the score. Athletes do not need a total score of 0 to return to play if they had symptoms before their concussion. This scale has not been validated to determine concussion severity.


A gold-standard assessment of suspected concussion has been difficult to ascertain throughout the years. Particularly difficult is the sideline evaluation where simply recognizing the injury can be most challenging for medical personnel. Initial sideline evaluation should include cervical spine stabilization, 4-limb neurologic testing, and evaluation of ABCs (airway, breathing, circulation). Secondly, discussion of the athlete's symptoms with an accepted sideline assessment tool (SCAT3 or Child-SCAT3) with balance testing should be completed because sensory coordination and vestibular systems are also affected by concussion. When available, preinjury baseline performance can be compared to the individual's postinjury test. Given the variability in concussion presentation, medical personnel are encouraged to err on the side of safety by adapting the phrase when in doubt, sit them out. If concussion is suspected, an athlete must be removed from participation and forbidden to return on the day of injury.

Evaluation with neuropsychologic testing provides another objective measurement of brain function. Computerized neurocognitive tests can be most useful to those familiar with the test and when athletes were able to perform baseline testing.

Concussion lacks structural changes with conventional imaging studies (MRI and CT) limiting their usefulness in evaluation. Neuroimaging should be used if suspicion of intracerebral lesion exists. Advances in functional neuroimaging have shown positive findings but require further research before clinical utilization and recommendation. Imaging may be indicated for possible related neck injury (see Chapter 689). CT imaging may be indicated for prolonged loss of consciousness, persistent altered mental status, focal neurologic deficits, suspicion of a skull fracture, or signs of clinical deterioration.

MANAGEMENT AND TREATMENT

Initial Phase

Management of a concussion also continues to evolve and is primarily based on symptom control while protecting the athlete from activities that may slow recovery. Initiating a management plan consisting of complete physical and cognitive rest is paramount. Symptoms may be followed with a postconcussion symptom scale (see Table 688-1), where symptoms are more likely to be reported. Concussed patients will often complain of increased symptoms with cognitive activities such as reading, video games, music, and even texting. They often have difficulty attending school, focusing on schoolwork, and trying to keep up with assignments. Taking standardized tests while recovering from a concussion is discouraged as lower-than-expected scores may occur. Cognitive rest may include shortened school days, reduced workload, or even temporary leave of absence with gradual return to school. Controlling symptoms can be difficult as there is no evidence-based pharmacologic treatment to offer a concussed athlete. However, medication is considered in those with prolonged recovery and specific symptoms. Vestibular therapy consisting of balance and oculomotor exercises has shown results in combating dizziness and vertigo. The duration of rest has been controversial, but one randomized controlled trial suggested that rest for 1-2 days when compared to 5 days resulted in fewer daily postconcussive symptoms and faster recovery.

Returning to Sport

No athlete should return to sport until clinically and completely asymptomatic at rest and without medication use. Each athlete's return should be individually based as recovery occurs at different rates with the majority of youth fully recovered by 1-3 wk; some may require 1-2 mo, particularly those who have had repeated concussions. Younger athletes may take longer to recover to neurocognitive and symptom baseline than older athletes. A return to play protocol provides a structured guideline that athletes progress through gradually, provided that the athlete remains asymptomatic for 24 hr at each step (Table 688-2). If no symptoms return, the athlete should wait 5 full days to complete and return to play. If symptoms have occurred, the athlete is required to rest until asymptomatic for 24 hr and resume at the previous asymptomatic step. It is important to consider individual factors at this juncture that are suspected to prolong recovery or increase patient
<table>
<thead>
<tr>
<th>REHABILITATION STAGE</th>
<th>FUNCTIONAL EXERCISE AT EACH STAGE OF REHABILITATION</th>
<th>OBJECTIVE OF EACH STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No activity</td>
<td>Symptom limited physical and cognitive rest</td>
<td>Recovery</td>
</tr>
<tr>
<td>2. Light aerobic exercise</td>
<td>Walking, swimming or stationary cycling keeping intensity &lt;70% maximum permitted heart rate No resistance training</td>
<td>Increase heart rate</td>
</tr>
<tr>
<td>3. Sport-specific exercise</td>
<td>Skating drills in ice hockey, running drills in soccer. No head impact activities</td>
<td>Add movement</td>
</tr>
<tr>
<td>4. Noncontact training drills</td>
<td>Progression to more complex training drills, e.g., passing drills in football and ice hockey May start progressive resistance training</td>
<td>Exercise, coordination and cognitive load</td>
</tr>
<tr>
<td>5. Full-contact practice</td>
<td>Following medical clearance participate in normal training activities</td>
<td>Restore confidence and assess functional skills by coaching staff</td>
</tr>
<tr>
<td>6. Return to play</td>
<td>Normal game play</td>
<td></td>
</tr>
</tbody>
</table>


susceptibility. Females may be at greater risk for concussion, increased severity, and longer duration of recovery.

After sustaining a concussion, a child is 2-6-fold more likely to sustain another concussion. This risk is heightened while recovering from an initial injury with a rare, yet catastrophic injury known as second-impact syndrome. In this injury, seen more frequently in child athletes, a mild impact may result in brain swelling and death. Previous and repeat concussions may be associated with slower recovery with more cognitive, emotional, physical, and sleep symptoms than those who have experienced 1 or no concussions.

Those with multiple concussions may experience a cumulative effect resulting in difficulty in attention and concentration. Prolonged concussive symptoms or postconcussion syndrome is another complication that is most simply noted as symptoms of concussion that persist beyond an expected time frame. Causes and correlations have yet to be determined, making this diagnosis difficult to establish.

**PREVENTION**

Despite ongoing research and technologic advances, personal protective equipment has not decreased the severity or reduced the incidence of concussion in team sports. Therefore, educating athletes, coaches, officials, and parents to adhere to rule changes should be emphasized. Concussion-related legislations may prove to be the most effective methods in managing and preventing concussion.

*Bibliography is available at Expert Consult.*
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Sports participation has surpassed motor vehicle crashes as the number 1 cause of cervical spine injuries in youth older than 9 yr of age. American football, hockey, and wrestling have the highest incidence in the United States; internationally, rugby is nearly as high.

The normal cervical spine has a lordotic curve, allowing it to absorb shock and dissipate force. When the neck is flexed forward, the spine straightens, losing this shock-absorbing property. Axial loading is when a force is applied to the top of the head in this flexed position transmitting force through the spine.

**SOFT-TISSUE INJURY**

The most frequent injury resulting from trauma to the head and neck involves the muscles, tendons, and ligamentous structures. Even though strains, sprains, and contusions are common, proper examination and evaluation is required to rule out more serious injuries. Even without bony abnormalities, the cervical spine may become unstable secondary to soft-tissue injury.

Spinal laxity results when most restraining ligaments are injured. When compared to adjacent vertebra, laxity should horizontally be less than 3.5 mm, and angular displacement less than 11 degrees on plain flexion/extension films. However, younger athletes have more baseline laxity making the criteria less applicable and muscle spasm can acutely mask instability. If subluxation is remotely suspected, a hard cervical collar should be placed and imaging obtained again at 2-4 wk when inflammation and spasm have subsided.

Disk injuries are rare in pediatric patients. Rupture or herniation must be considered in any cervical pain differential (see Chapter 679.8).

**SPEAR TACKLER’S SPINE**

This clinical entity is characterized by progressive spinal changes secondary to incorrect tackling form. Findings on plain x-ray consist of (1) narrowing of cervical spinal canal, (2) loss or reversal of normal cervical lordosis, and (3) preexisting minor posttraumatic x-ray evidence of bony or ligamentous injury. Although rule changes in collision and contact sports have limited the practice of making contact with a “head-down” neck position, this condition still persists.

Many experts argue that this condition disqualifies athletes from return to play. Others argue that if physical therapy and rehabilitation are able to correct the curvature and improper technique is corrected, then athletes are not at a high risk of reinjury and could return. Data are lacking and more research required for a definitive answer.

**CERVICAL FRACTURES**

All significant neck injuries should be treated seriously until cleared with appropriate examination and imaging. Although many cervical fractures are stable, improper management or inadequate evaluation could end with catastrophic results. Until properly evaluated, the patient should be immobilized and treated as if the patient has an unstable cervical fracture.

**STINGERS (BURNERS)**

Stingers are unilateral peripheral nerve injuries occurring somewhere between the cervical nerve root and the brachial plexus. Three
PROPOSED MECHANISMS FROM ELECTROPHYSIOLOGY AND FUNCTIONAL IMAGING STUDIES OF CERVICAL SPINE INJURIES

proposed mechanisms are traction or tensile stretch injury, compressive injury, and direct trauma. Typical presentation is a transient episode of unilateral pain, with or without paresthesia, in an upper extremity. Symptoms of C5 and C6 roots and upper trunk are most common. Careful examination for weakness should be performed, especially shoulder abduction, external rotation, and elbow flexion. Cervical spine should have pain-free full range of motion and have no tenderness to palpation. Spurling’s Compression test, a head-tilting maneuver that when positive differentiates cervical radiculopathy from other causes of upper-extremity pain, may or may not be positive. The test is only 30% sensitive, but specificity is 93%.

Return to play may be considered the same day if the exam is reassuring. This requires complete resolution of symptoms, full range of motion, and normal strength. Multiple stingers, bilateral symptoms, or symptoms persisting for longer than 1 hr should prompt further evaluation before resumption of any physical activities.

**TRANSIENT QUADRIPARESIS**

Transient quadriplegiasis (TQ) is a temporary neurologic episode encompassing sensory symptoms with or without motor changes. TQ is also known as **cervical cord neurapraxia**, **burning hands syndrome**, **commotio spinalis**, and **spinal cord concussion**. TQ can be divided into 3 types: plegia (complete loss of motor function), paresis (motor weakness), and paresthesia (sensory symptoms only). There is also a 3-part grading system: grade 1 symptoms last <15 min, grade 2 symptoms last 15 min to 24 hr, and grade 3 symptoms persist beyond 24 hr. TQ must be differentiated from just a stinger and the player should be removed from activity and spinal injury considered.

Mechanisms of injury include hyperextension, hyperflexion, and axial loading. Anatomically, when the neck is hyperflexed or hyperextended, the spinal canal is narrowed by up to 30%, increasing the likelihood of cord injury.

*Burning hands syndrome* is the most common presentation. The athlete has intense paresthesias in both upper extremities. This is suggestive of a central cord syndrome and includes burning, tingling, and loss of sensation. Treat athletes with full cervical precautions to prevent injury progression.

Evaluation should start with plain flexion and extension films if stable. CT can be utilized if cervical fracture is suspected. MRI should then be used to evaluate for intrinsic spinal cord abnormalities or ongoing cord or root compression. Spinal stenosis is discussed below.

Return to play for TQ is heavily debated and lacks data to support it. Conservatively, some argue that 1 is a contraindication to return to contact sports, whereas others agree with utilizing the *Return to Play Table* (Table 689-1) for absolute and relative contraindications for return. If allowed to return to play and second episode of TQ occurs, the complete work-up needs repeating.

**CONGENITAL SPINAL STENOSIS**

Developmental narrowing of the cervical spinal canal predisposes an athlete to higher risk of spinal cord injury. This condition can be found incidentally while working up other conditions. The Torg Ratio, the ratio of vertebral body width to canal width on plain lateral film (cutoff for normal is 0.7 or 0.8, depending on clinical setting), is being evaluated for utility as a diagnostic test. Alternatively, a canal width measurement <13 mm between C3 and C7 can be used to define stenosis, with “normal” being >15 mm.

*Functional stenosis* can be seen with dynamic MRI in flexion and extension to see if the canal space decreases with movement. The positioning of the canal in flexion or extension causes narrowing from positioning of the vertebra and ligament, respectively. The measured diameter may be irrelevant if disc protrusion or ligament hypertrophy causes compression. This narrow “reserve space” around the spinal cord puts the athlete at greater risk for injury as compared to the same force on a normal spine.

**SPINAL CORD INJURY**

Spinal cord injury is the most dreaded complication of cervical trauma and is categorized into 4 entities. Hemorrhage and transection are

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**Table 689-1 Return to Play (RTP) Table**

<table>
<thead>
<tr>
<th>NO CONTRAINDICATION TO RTP</th>
<th>Healed fractures including:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing C1 or C2 fracture with normal cervical spine range of motion (ROM)</td>
<td></td>
</tr>
<tr>
<td>Healing subaxial fracture without sagittal plane deformity</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic clay-shoveler’s (C7) spinous process avulsion fracture</td>
<td></td>
</tr>
<tr>
<td>Klippel-Feil (single-level anomaly not C0/C1 articulation)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Congenital conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina bifida occulta</td>
</tr>
<tr>
<td>Cervical disc disease (no change in baseline neurologic status)</td>
</tr>
<tr>
<td>Single-level anterior cervical fusion (ACF) with/without instrumentation</td>
</tr>
<tr>
<td>Single- or multiple-level posterior cervical laminotomy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Degenerative/postsurgical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single episode</td>
</tr>
<tr>
<td>Full cervical range of motion</td>
</tr>
<tr>
<td>Normal neurologic exam</td>
</tr>
<tr>
<td>No radiologic instability</td>
</tr>
<tr>
<td>Normal spinal reserve (as evidenced on MRI)</td>
</tr>
</tbody>
</table>

**RELATIVE CONTRAINDICATION TO RTP**

<table>
<thead>
<tr>
<th>Stingers/Burners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged symptomatic burner/stinger</td>
</tr>
<tr>
<td>Three or more stingers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transient quadriplegiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient quadriplegiasis lasting &gt;24 hr</td>
</tr>
<tr>
<td>More than 1 episode with symptoms of any duration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postsurgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healed 2-level ACF</td>
</tr>
<tr>
<td>Posterior cervical fusion (PCF) with/without instrumentation</td>
</tr>
</tbody>
</table>

**ABSOLUTE CONTRAINDICATION TO RTP**

<table>
<thead>
<tr>
<th>Transient quadriplegiasis and any 1 or more of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical myelopathy</td>
</tr>
<tr>
<td>Continued neck discomfort</td>
</tr>
<tr>
<td>Reduced ROM</td>
</tr>
<tr>
<td>Neurologic deficit from baseline after injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 + C2 fusion</td>
</tr>
<tr>
<td>Cervical laminectomy</td>
</tr>
<tr>
<td>Three-level ACF or PCF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Soft-tissue injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic ligamentous laxity (&gt;11 degrees of kyphotic deformity)</td>
</tr>
<tr>
<td>C1 + C2 hypermobility with anterior dens &gt;3.5 mm (adult), &gt;4 mm (child), i.e., Down syndrome (see Chapter 680)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other conditions including:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spear tacker’s spine</td>
</tr>
<tr>
<td>Multilevel Klippel-Feil anomaly (see Chapter 680)</td>
</tr>
<tr>
<td>Healed subaxial fracture with sagittal kyphosis coronal plane abnormality, or cord encroachment</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Rheumatoid arthritis with spinal abnormalities</td>
</tr>
<tr>
<td>Spinal cord abnormality (cord edema, compression, etc.)</td>
</tr>
<tr>
<td>Arnold-Chiari syndrome</td>
</tr>
<tr>
<td>Basilar invagination</td>
</tr>
<tr>
<td>Occipital-C1 assimilation</td>
</tr>
<tr>
<td>Occipitalization or connection</td>
</tr>
<tr>
<td>Spinal stenosis (canal width &lt;13 mm between C3 and C7)</td>
</tr>
</tbody>
</table>

considered irreversible and associated with complete cord injury, whereas contusion and edema (Fig. 689-1) are considered to have more potential for recovery. Steroids and hypothermia are 2 proposed treatments to prevent secondary injury. These severe injuries should be managed by providers with expertise in this area.

*Bibliography is available at Expert Consult.*
Bibliography
Heat illness is the third leading cause of death in U.S. high school athletes. It is a continuum of clinical signs and symptoms that can be mild (heat stress) to fatal (heatstroke) (see Chapter 70). Children are more vulnerable to heat illness than adults because they have greater ratio of surface area to body mass and produce greater heat per kilogram of body weight during activity. The sweat rate is lower in children and the temperature at which sweating occurs is higher. Children can take longer to acclimatize to warmer, more humid environments (typically 8-12 near-consecutive days of 30-45 min exposures). Children also have a blunted thirst response compared to adults and might not consume enough fluid during exercise to prevent dehydration.

Three categories for heat illness are generally used: heat cramps, heat exhaustion, and heat stroke (Table 690-1). However, symptoms of heat illness overlap and advance as the core temperature rises. Heat cramps are the most common heat injury and usually occur in mild dehydration and/or salt depletion, usually affecting the calf and hamstring muscles. They tend to occur later in activity, as muscle fatigue is reached and water loss and sodium loss worsen. They respond to oral rehydration with electrolyte solution and with gentle stretching. The athlete can return to play when ability to perform is not impaired.

Heat syncope is fainting after prolonged exercise attributed to poor vasomotor tone and depleted intravascular volume, and it responds to fluids, cooling, and supine positioning. Heat edema is mild edema of the hands and feet during initial exposure to heat; it resolves with acclimatization. Heat tetany is carpopedal tingling or spasms caused by heat-related hyperventilation. It responds to moving to a cooler environment and decreasing respiratory rate (or rebreathing by breathing into a bag).

Heat exhaustion is a moderate illness with core temperature 37.7-39.4°C (100-103°F). Performance is obviously affected, but central nervous system dysfunction is mild, if present. It is manifested as headache, nausea, vomiting, dizziness, orthostasis, weakness, piloerection, and possibly syncope. Treatment includes moving to a cool environment, cooling the body with fans, removing excess clothing, and placing ice over the groin and axillae. If a patient is not able to tolerate oral rehydration, IV fluids are indicated. Patients should be monitored, including rectal temperature, for signs of heat stroke. If rapid improvement is not achieved, transport to an emergency facility is recommended.

Heat stroke is a severe illness manifested by central nervous system disturbances and potential tissue damage. It is a medical emergency; the mortality rate is 50%. Sports-related heat stroke is characterized by profuse sweating and is related to intense exertion, whereas “classic” heatstroke with dry, hot skin is of slower onset (days) in elderly or chronically ill persons. Rectal temperature is usually >40°C (104°F). Significant damage to the heart, brain, liver, kidneys, and muscle occurs, with possible fatal consequences if untreated. Treatment is immediate whole-body cooling via cold water immersion. Airway, breathing, circulation, core temperature, and central nervous system status should be monitored constantly. Rapid cooling should be ceased when core temperature is approximately 38.3-38.9°C (101-102°F). IV fluid at a rate of 800 mL/m² in the 1st hr with normal saline or lactated Ringer solution improves intravascular volume and the body's ability to dissipate heat. Immediate transport to an emergency facility is necessary. Physician clearance is required before return to exercise.

Dehydration is common to all heat illness; consequently, measures to prevent dehydration can also prevent heat illness. Thirst is not an adequate indicator of hydration status because it is initiated at 2-3% dehydration. Athletes are advised to be well hydrated before exercise and should drink every 20 min during exercise (5 oz for those who...
Heat necessary to replace (8 oz for each pound of weight loss). Proper clothing such as shorts and T-shirts weighing 40 kg, 9 oz for 60 kg, and 10-12 oz for those >60 kg). Free access to cold water should be advocated to coaches. During a football practice, scheduled breaks every 20-30 min with helmets off to get out of the heat can decrease the cumulative amount of heat exposure. Practices and competition should be scheduled in the early morning or late afternoon to avoid the hottest part of the day. Guidelines have been published about modifying activity related to temperature and humidity (Fig. 690-1). Proper clothing such as shorts and T-shirts without helmets can improve heat dissipation. Prepractice and postpractice weight can be helpful in determining the amount of fluid necessary to replace (8 oz for each pound of weight loss).

Water is adequate for most persons who exercise <1 hr, although there is evidence that children drink more water when it is flavored. Fluids with electrolyte and carbohydrate are more important for persons who exercise for longer than 1 hr. Salt pills should not be used by most people because of the risk of their causing hypernatremia and delayed gastric emptying. They may be useful in a person with a high sweat rate or recurrent heat cramps. Prolonged exercise (marathon running) with only water replacement places the athlete at risk of hyponatremia.

Bibliography is available at Expert Consult.
Bibliography

Physical training in young women can adversely affect reproductive function and bone mineral status especially when combined with calorie restriction (see Chapters 28 and 116).

The majority of bone mass is acquired by the end of the 2nd decade (see Chapter 707). Approximately 60-70% of adult bone mass is genetically determined, and the remaining is influenced by 3 controllable factors: exercise, calcium intake, and sex steroids, primarily estrogen. Exercise promotes bone mineralization in the majority of young women and is to be encouraged. In girls with eating disorders and those who exercise to the point of excessive weight loss with amenorrhea or oligomenorrhea, exercise can be detrimental to bone mineral acquisition, resulting in reduced bone mineral content, or osteopenia.

Specifically, bone mineralization is negatively affected by amenorrhea (absence of menstruation for $≥3$ consecutive months). This may be influenced by abnormal eating patterns, or “disordered eating.” When occurring together, disordered eating, amenorrhea, and osteoporosis form the female athlete triad. At health supervision visits and the preparticipation physical examination, special attention should be given to screening for any features of the triad.

Menstrual abnormalities (including amenorrhea) result from suppression of the spontaneous hypothalamic pulsatile secretion of gonadotropin-releasing hormone (see Chapter 116.1). It is believed that the amenorrhea results from reduced energy availability, defined as energy intake minus expenditure. Energy availability below a threshold of 30 kcal/kg/day lean body mass is thought to result in menstrual disturbances. Negative energy balance also appears to lower levels of leptin, which affects both nutritional state and the reproductive system. Other causes to be ruled out are pregnancy (see Chapter 118), pituitary tumors, thyroid abnormalities, polycystic ovary syndrome (see Chapter 552), anabolic–androgenic steroid use (see Chapters 114 and 692), and other medication side effects.

The low estrogen state of amenorrhea predisposes the female athlete to osteopenia and puts her at risk for stress fractures, especially of the spine and lower extremity. If left unchecked, bone loss is partially irreversible despite resumed menses, estrogen replacement, or calcium supplements. Routine bone mineral density screening is not recommended but can help guide treatment and return to activity in severe cases.

Normal ovulation and menses can be recovered in athletes with amenorrhea. This usually involves decreasing exercise amount and/or increasing caloric intake. However, many athletes are resistant to a decrease their training, and other methods, such as hormone supplementation, should be discussed. Nutritional counseling is important to help the athlete develop a plan for increasing calories. Calcium intake should be addressed, with the goal being at least $1,500$ mg daily. If amenorrhea is present for $≥6$ mo, hormone supplementation is recommended.

Three eating disorders can occur in the context of amenorrhea. Anorexia nervosa manifests as weight $<85\%$ of estimated ideal body weight with evidence of starvation manifesting as bradycardia, hypothermia, and orthostatic hypotension or orthostatic tachycardia. Bulimia nervosa manifests as recurrent episodes (at least once weekly) of binge eating with a sense of lack of control over eating during an episode with recurrent episodes of compensatory behaviors. A third category, "Unspecified Feeding and Eating Disorder," is a general description for disorders failing to meet the criteria for the 2 previous disorders. With the revised diagnostic criteria for bulimia and anorexia nervosa in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, it is anticipated that many young women who previously were diagnosed as “Unspecified Feeding and Eating Disorder” will receive a specific diagnosis of anorexia or bulimia. Signs of an eating disorder are weight loss, food restriction, depression, fatigue, and worsened athletic performance, and preoccupation with calories and weight. The athlete might avoid events surrounding food consumption or might hide and discard food. Signs and symptoms include fat depletion, muscle wasting, bradycardia worsened from baseline, orthostatic hypotension, constipation, cold intolerance, hypothermia, gastric motility problems, and, in some cases, lanugo (see Chapter 28). Electrolyte abnormalities can lead to cardiac dysrhythmias. Psychiatric problems (depression [see Chapter 26], anxiety [see Chapter 25], suicide risk [see Chapter 27]) are of higher incidence in this population.

For treatment of eating disorders, control of the symptoms is a central theme. The first step is confronting the athlete about the abnormal behavior and unhealthy weight. Generally, exercise is not recommended if the body weight is $<85\%$ of estimated ideal body weight, although there are exceptions, especially if the athlete is eumenorrheic. If the athlete is unable to gain weight with nutrition and medical counseling alone, then psychologic consultation is sought.

Most athletes will not initially admit a problem, and many are unaware of the serious physical consequences. A helpful technique in talking to these athletes is to sensitively point out performance issues. Education about decreased strength, endurance, and concentration can be a motivating factor for treatment. Often, the athlete's family needs to be involved, and the athlete should be encouraged to reveal necessary information to them. Psychology or psychiatry referral is important in the multidisciplinary approach to treatment of disordered eating. It is important for the physician to monitor the athlete's physical health while the mental health professional is caring for the mental aspects of the eating disorder.

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Ergogenic aids are substances used for performance enhancement, most of which are unregulated supplements (Table 692-1). The 1994 Dietary Supplement and Health Education Act limited the ability of the U.S. Food and Drug Administration to regulate any product labeled as a supplement. Many agents have significant side effects without proven ergogenic properties. In 2005, the American Academy of Pediatrics published a policy statement strongly condemning their use in children and adolescents. The 2004 Controlled Substance Act outlawed the purchase of steroidal supplements such as androstenediol, and androstenedione, with the exception of dehydroepiandrosterone (DHEA).

The prevalence of lifetime steroid use is highest among boys in the United States; among a large representative sample in 2010, 5.5% of
Table 692-1  Ergogenic Drugs

<table>
<thead>
<tr>
<th>ERGOGENIC DRUG</th>
<th>CATEGORY</th>
<th>GOALS OF USE</th>
<th>ATHLETIC EFFECT</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic–androgenic steroids</td>
<td>Controlled substance</td>
<td>Gain muscle mass, strength</td>
<td>Increase muscle mass, strength</td>
<td>Multiple organ systems: infertility, gynecomastia, female virilization, hypertension, atherosclerosis, physeal closure, aggression, depression</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>Controlled substance</td>
<td>Increase testosterone to gain muscle mass, strength</td>
<td>No measurable effect</td>
<td>Increase estrogens in men; overlaps systemic risks with steroids</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>Nutritional supplement</td>
<td>Increase testosterone to gain muscle mass, strength</td>
<td>No measurable effect</td>
<td>Increase estrogens in men; impurities in preparation</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Controlled substance</td>
<td>Increase muscle mass, strength, and definition</td>
<td>Decreases subcutaneous fat; no performance effect</td>
<td>Acromegaly effects: increased lipids, myopathy, glucose intolerance, physeal closure</td>
</tr>
<tr>
<td>Creatine</td>
<td>Nutritional supplement</td>
<td>Gain muscle mass, strength</td>
<td>Increase muscle strength gains; performance benefit in short, anaerobic tasks</td>
<td>Dehydration, muscle cramps, gastrointestinal distress, compromised renal function</td>
</tr>
<tr>
<td>Ephedra alkaloids</td>
<td>Possibly returning as nutritional supplement</td>
<td>Increase weight loss, delay fatigue</td>
<td>Increases metabolism; no clear performance benefit</td>
<td>Cerebral vascular accident, arrhythmia, myocardial infarction, seizure, psychosis, hypertension, death</td>
</tr>
</tbody>
</table>


Boys in middle school and 6.6% of those in high school report having used steroids for muscle-enhancement. The European School Survey Project on Alcohol and Other Drugs found that 1% of European youth reported any use of steroids. Steroids in oral, injectable, and skin cream form are taken in various patterns. Cycling is a term used to describe taking multiple doses of steroids for a period, ceasing, and then starting again. Stacking refers to the use of different types of steroids in both oral and injectable forms. Pyramiding involves slowly increasing the steroid dose to a peak amount and then gradually tapering down.

Anabolic–androgenic steroids have been used in supraphysiologic doses for their ability to increase muscle size and strength and decrease body fat. An evidence-base does support the increase in muscle mass and strength; the effects appear to be related to the myotropic action at androgen receptors as well as competitive antagonism at catabolism-mediating corticosteroid receptors. However, they have significant endocrinologic side effects, such as decreased sperm count and testicular atrophy in men and menstrual irregularities and virilization in women. Hepatic problems include elevated aminotransaminases and γ-glutamyl transferase, cholesstatic jaundice, peliosis hepatitis, and a variety of tumors, including hepatocellular carcinoma. There is evidence that anabolic–androgenic steroids might cause cardiovascular problems as well, including higher blood pressure, lower high-density lipoprotein, higher low-density lipoprotein, higher homocysteine, and decreased glucose tolerance. The psychologic effects include aggression, several personality disorders, and a variety of other psychologic problems (anxiety, paranoia, mania, depression, psychosis). Physical findings in males include gynecomastia, testicular shrinkage, jaundice, male pattern baldness, acne, and marked striae. Women can develop hirsutism, voice deepening, cliterol hypertrophy, male-pattern baldness, acne, and marked striae.

Testosterone precursors (also known as prohormones) include androstenedione and DHEA. Their use in the adolescent population has increased markedly in conjunction with reports of high-profile athletes’ use. They are androgenic but have not been proved to be anabolic. If they are anabolic at all, they work by increasing the production of testosterone. They also increase production of estrogenic metabolites. The side effects are similar to those of anabolic–androgenic steroids and far outweigh any ergogenic benefit. Since January 2005, these substances cannot be sold without prescription.

Creatine is an amino acid mostly stored in skeletal muscle. Its key feature is ability to rephosphorylate adenosine diphosphate to adenosine triphosphate, therefore increasing muscle performance. Its use has increased, especially since other supplements have been withdrawn from the market. Thirty percent of high school football players have used creatine. There is evidence that creatine, as a source of increased energy, enhances strength and maximal exercise performance when used during training. There is no evidence that creatine affects hydration or temperature regulation. Concerns about nephritis in case reports have not been supported by controlled studies. However, there are few long-term studies evaluating creatine use.

Caffeine is an active ingredient in energy drinks and some endurance sport supplements. More of a problem as an energy drink when combined with alcohol, excessive caffeine ingestion may result in tachycardia, gastritis, nausea, vomiting, and central nervous system excitation. Overdoses may result in seizures, arrhythmias, and hypotension.

Bibliography is available at Expert Consult.
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GYMNASTICS

Typically, males and females begin gymnastics participation at 4-5 yr of age. The highest level of competition is in the mid-teens followed by retirement, often by 20 yr for females and mid-twenties for males. Lower-extremity injuries are more common in female gymnasts,
whereas upper body injuries occur with higher frequency in male gymnasts. Apparatus competed upon accounts for this discrepancy, such as the horizontal bar and ring exercises for male gymnasts, which place a great deal of stress upon the shoulders. In addition to mechanical or traumatic injuries, female gymnastics commonly have delayed menarche and are at risk for hypothyroidism or oligomenorrhea, as well as low body weight for height related to disordered eating. Despite the presence of these 2 components of the female athlete triad (see Chapter 691), the third component, reduced bone density or osteoporosis, is not commonly seen. In fact, bone density tends to be high in most gymnasts, which is thought to be secondary to their performance involving repetitive high-impact activities. Nevertheless, stress fractures, in both the upper and lower extremities, are a significant problem. The short stature associated with male and female gymnasts is probably caused by selection bias and not the result of gymnastics training.

Both acute and chronic injuries are seen in gymnasts and commonly involve the ankles, wrists, and spine. The incidence of injury increases with the skill level and is greatest with the floor exercise. The amount of weightbearing through the upper extremities in gymnastics lends itself to the development of both traumatic and overuse injuries. At the wrist, this can manifest as Salter I stress fractures of the distal radial physis (gymnast’s wrist), triangular fibrocartilage tears, scaphoid fractures, dorsal ganglions, and, most commonly, wrist sprains (see Chapter 683.2). Spine injuries are notable for a high incidence of spondylolysis (stress fracture of the pars interarticularis) and, in less frequent cases, spondylolisthesis, both related to repetitive extension loading of spine (see Chapter 679.6). Ligamentous laxity can predispose to elbow or shoulder dislocation and ankle sprains.

Treatment of many of these injuries includes relative rest from the inciting activity, immobilization, ice, and nonsteroidal antiinflammatory drugs. Imaging begins with radiographs but may include bone scan with single-photon emission computed tomography to evaluate spondylolysis, or MRI to rule out intraarticular tears, loose bodies, ligamentous instability, or physeal injury. A pediatrician should have a low threshold for referral to a sports medicine or orthopedic specialist in a child with a wrist injury not improving with rest.

**SWIMMING**

Injuries of the shoulder in competitive swimming are most common and generally a result of chronic, overuse. Swimmer’s shoulder is a combination of subacromial bursitis and tendinosis of the rotator cuff and long-head of the biceps. Commonly, increased laxity of the shoulder capsule and weakness of the scapular stabilizers contribute over time leading to the insidious onset of shoulder pain (see Chapter 687.2). Freestyle, back, and butterfly strokes tend to exacerbate the pain. Pain may be provoked on exam by passively abducting the arm to 90 degrees, forward flexing to 30 degrees, and internally rotating the humerus with the elbow extended while having the patient actively abduct against resistance (Empty Can Test). The Hawkins impingement test involves the same position of the shoulder with the elbow flexed to 90 degrees and the examiner internally rotating the humerus. Pain and/or weakness indicates supraspinatus injury. Treatment includes relative rest, ice, and modification of stroke technique. The multi-axial instability of the glenohumeral joint common to swimmers is addressed with rehabilitation focusing upon strengthening of the rotator cuff and scapular stabilizer musculature. Prevention includes monitoring training load, proper technique and strengthening exercises.

Swimmer’s ear, or otitis externa, presents with pain and often drainage from the external auditory canal. It is caused by bacterial, or less commonly, fungal infection of the external auditory canal due to chronic, excessive wetness (see Chapter 639).

**BASEBALL**

Throwing injuries of the elbow and shoulder (particularly among pitchers) are the most common baseball injuries (see Chapters 687.2 and 687.3). Monitoring the number of pitches thrown per game, no more than 6 times the young athlete’s age in years and per week based upon the athlete’s age, is important. Counseling athletes (and coaches) to stop all throwing activities if the player experiences elbow pain, with medical evaluation to be sought if there is no resolution with rest, is essential. Death or serious injury in baseball is rare and generally from direct contact by the ball, causing serious head injury or, in the case of chest wall impact, commotio cordis. Batting helmets need to be worn properly to try to prevent face and head injuries; modifications to the hardness of baseballs used with younger athletes is also helpful. Injuries to catchers can involve traumatic brain injury with various levels of concussion from contact of the ball to the face mask. Catchers are more vulnerable to traumatic sprains of the interphalangeal and metacarpal phalangeal joints along with internal derangement and ligamentous sprain of the knees associated with the deep squatting posture.

**DANCE**

Dance is a highly demanding activity that may be associated with delayed menarche and disordered eating in females (see Chapter 691). Acute injuries commonly involve the lower extremities. Overuse injuries are likely, due to the repetitive nature of maneuvers incorporated into training and performance. Frequently, kinetic chain dysfunction contributes to injury and this should be considered when evaluating the dancer. Common mistakes in technique can cause injury, such as forcing excessive “turnout” (external rotation at the hip) in ballet can result in undue stress being placed upon the knees (see Chapter 687.6). An unrehabilitated ankle sprain may cause favoring of the affected leg leading to development of a stress fracture of the contralateral tibia. In contrast to injuries in most types of dance, injuries associated with breakdancing more frequently involve the spine and upper extremities than lower extremities. This likely relates to the significant amount of twisting of the torso and weight bearing through the hands inherent in this genre of dance.

Foot problems are not uncommon and include metatarsal stress fractures, subungual hematomas, sesamoiditis, plantar fasciitis, calluses, and bunions (see Chapter 687.9). A Dancer’s fracture is an avulsion fracture of the distal shaft of the 5th metatarsal. This is treated with immobilization for 4-6 wk, although poor healing, a result of the tenuous blood supply in the area, may necessitate surgical fixation. Common ankle injuries include acute sprains, anterior and posterior impingement syndromes, and osteochondritis dissecans of the talus. Medial tibial stress syndrome (“shin splints”) and tibial stress fractures are noted in the lower leg. Patellar malalignment/hypermobility can result in patellofemoral pain syndrome or, less frequently, patellar subluxation/dislocation. Medial snapping hip syndrome, caused by the iliotibial band riding over the anterior hip capsule, and hip flexor (rectus femoris, iliopsoas) tendinosis are commonly noted in addition. Gluteal region pain with sciatica may be a result of piriformis syndrome, which occurs because of the repetitive external hip rotation required in ballet (see Chapter 687.5). The proper timing of allowing a ballet dancer to go en pointe is a common question asked by dancers and parent alike. An average age to go en pointe is 12 yr. A functional test should be part of that decision: If the young dancer is able to perform a passé steadily away from the barre to stop all throwing activities if the player experiences elbow pain, with medical evaluation to be sought if there is no resolution with rest, is essential. Death or serious injury in baseball is rare and generally from direct contact by the ball, causing serious head injury or, in the case of chest wall impact, commotio cordis. Batting helmets need to be worn properly to try to prevent face and head injuries; modifications to the hardness of baseballs used with younger athletes is also helpful. Injuries to catchers can involve traumatic brain injury with various levels of concussion from contact of the ball to the face mask. Catchers are more vulnerable to traumatic sprains of the interphalangeal and metacarpal phalangeal joints along with internal derangement and ligamentous sprain of the knees associated with the deep squatting posture.

**WRESTLING**

Wrestlers have great fluctuations in weight to meet weight-matched competition standards. Such fluctuations are associated with fasting, dehydration, and then binging. Counseling to wrestlers and their parents regarding impaired performance resulting from these components of disordered eating, especially with respect to decreased speed and strength, is important in order to deter athletes from incorporating them into routine practice.

Wrestling holds apply a variety of torques or forces to the extremities and spine producing a number of common injuries. Takedown maneuvers and subsequent impact with the mat can produce concussions, neck strain/sprain, or spinal cord injury (see Chapter 689). Stingers and burners, also seen among football players, are caused by stretching or pinching of the brachial plexus (see Chapter 689). Pain at the shoulder...
often radiates down the arm and is frequently associated with paresthesias and weakness; the latter most commonly involving the deltoid and other C5/C6 innervated muscles. Overall, the 2 most common sites of injury in wrestling are the shoulder and knee.

At the shoulder, subluxation is common. This generally occurs anteriorly with the shoulder forcibly abducted and extended. Patients are commonly aware of their shoulder slipping in and out (see Chapter 687.2).

Injuries to the hand are less common and typically include metacarpophalangeal and proximal interphalangeal joint sprains. Treatment consists of buddy taping and/or splinting.

Knee injuries (see Chapter 687.6) are also common and include prepatellar bursitis, medial and lateral collateral ligament sprains, and medial and lateral meniscus tears. Acute or recurrent traumatic impact to the mat can result in prepatellar bursitis. Swelling is noted over the patella with the patient experiencing limitations to range of motion primarily with knee flexion as a result. If the overlying skin is broken, septic bursitis must be considered. Distinguishing between a traumatic and infected bursitis may require aspiration of the bursa. Treatment of traumatic bursitis includes protective padding upon return to wrestling, ice, nonsteroidal antiinflammatory drugs (NSAIDs), and, on occasion, aspiration if flexion is markedly impaired. Recurrence after aspiration is not uncommon. Rarely, bursectomy is needed if there are several recurrences.

Dermatologic problems associated with wrestling include herpes simplex (see Chapter 252: herpes gladiatorum), impetigo (see Chapter 665.1), staphylococcal furunculosis or folliculitis, superficial fungal infections, and contact dermatitis. Herpes gladiatorum and impetigo are contraindications to wrestling until the lesions have resolved. Treatment of herpes gladiatorum with oral antiviral medications, such as Acyclovir, for both acute outbreaks and long-term suppression is recommended. Washing of the wrestling mats with appropriate antibacterial and antifungal solution is required after daily wrestling sessions to keep the mats disinfected and protect the spread of dermatologic contagion.

Auricular hematoma is caused by friction or direct trauma to the auricle (see Chapter 642). If allowed to remain without evacuation, irreversible deformity of the auricle often results, termed cauliflower ear. Properly fitted headgear is the best means of prevention.

**FOOTBALL**

Football is the sport with the highest number of injuries, with the greatest number of participants (especially at the high school level) and with a higher rate of injury. The majority of these injuries is relatively minor and compared to many other sports, the injuries are less severe, as evidenced by less number of days lost from injury. The most common football injuries include joint sprains, muscle strains, and contusions, with the lower extremities injured most frequently. Treated appropriately, these injuries generally result in minimal time away from football. An important exception to this, contusions to the arm or thigh muscles can result in the development of a large hematoma if not treated aggressively in the acute stage, resulting in prolonged time away from football. Without the presence of fracture, treatment includes ice and compression for the 1st few days to reduce the expansion of the hematoma. Pain-free stretching and strengthening exercises are then incorporated. Therapeutic ultrasound per physical therapy staff can be helpful in stretching deeper tissue and resolving persistent hematoma limiting further flexibility. Return to contact play is initiated when baseline range of motion and strength are achieved. Large hematomas and those allowed to persist are at risk for development of myositis ossificans.

Although the majority of catastrophic sports injuries in the United States have occurred in football, these injuries are rare. Catastrophic injury is defined as a fatal injury or a severe injury with or without permanent severe functional disability. Disabling injuries include cervical spine and cerebral injuries.

Head and neck injuries in football include concussion, neck sprain, and brachial plexopathy. The latter, also seen among wrestlers, is referred to as a stinger or burner and represents a brachial plexus neurapraxia (see Chapter 689). This is the most common nerve injury in football and is often the result of a traction or compression injury to the upper nerve roots of the brachial plexus caused by forceful lateral neck bending. This results in painful arm dysesthesias and deltoid muscle weakness. This is usually transient, resolving in minutes to days, with return to play upon return of full range of motion, comfort and strength.

Compared to other sports, brain injury (concussions) occurs with the highest rate in football, a result of the frequent exposure to contact during practices and games. The prevention, diagnosis, and management of this significant injury with potentially lifelong implications are discussed in full in Chapter 688.

Lumbar spine injury manifested as low back pain can indicate spondylolysis (see Chapter 679.6). Shoulder trauma can cause glenohumeral dislocation, the majority of which are anterior dislocations, acromioclavicular joint sprain, and fractures to the clavicle or humerus (see Chapter 687.8). Knee injuries (see Chapter 687.6) are common and include anterior cruciate ligament and, less frequently, posterior cruciate ligament tears along with medial collateral ligament sprains.

Ankle sprains occur frequently, and the risk of reinjury may be reduced by rehabilitation and the use of a lace-up ankle brace (see Chapter 687.6). Turf toe, a sprain to the 1st metatarsophalangeal joint, is caused by forceful dorsiflexion of the toe while wearing soft, lightweight, flexible shoes. Treatment of turf toe includes ice, NSAIDs, and orthotic to limit extension of the great toe, along with rest.

**ICE HOCKEY**

Ice hockey is classified as a collision sport and is associated with injuries caused by contact from the puck or stick as well as from other players, the ice, or the boards. These injuries commonly include contusions, lacerations, fractures, sprains, or concussions. The risk of injury is reduced by the use of proper equipment (helmets with facemasks) and enforcement of the rules regarding dangerous body contact (checking from behind, high sticking, and fighting).

Specific hockey injuries include ankle sprains (dorsiflexion, eversion, and external rotation in contrast to the usual inversion sprain in other sports), hip adductor strain, osteitis pubis, and various shoulder injuries from body contact. The latter include acromioclavicular joint sprain, glenohumeral dislocation, and clavicle fractures (see Chapter 687.2). The most serious injuries are to the head and neck (see Chapters 688 and 689).

**BASKETBALL AND VOLLEYBALL**

Common maneuvers of these 2 sports include jumping, pivoting, running and sudden stopping which increase the risk for knee and ankle injuries. Similarly, injury to the fingers may result from the passing, catching, and striking of the ball inherent in these sports.

Knee injuries include those caused by overuse, such as traction apophysisis (Osgood-Schlatter disease) and patellar tendinosis (jumper’s knee) (see Chapter 687.6). As with other jumping sports, acute ligament sprains (medial collateral with or without anterior cruciate ligaments) can occur. Shoulder injuries in volleyball players are similar to other overhead athletes and include rotator cuff tendinosis and glenohumeral instability.

**Ankle sprain** is the most common injury and is usually caused by inversion with plantar flexion, placing the lateral ligaments at high tension. An avulsion fracture of the base of the 5th metatarsal at the insertion of the peroneus brevis tendon is another sequela of inversion ankle injuries. In terms of overuse injuries at the ankle, Achilles tendinosis is common. Foot pain may be from calcaneal apophysitis (Sever disease), retrocalcaneal bursitis, posterior tibialis tendinosis, accessory tarsal navicular, plantar fasciitis, stress fracture of the tarsal navicular, Jones’s stress fracture of the 5th metatarsal, sesamoiditis, blisters, subungual hematoma, and paronychia (see Chapters 687.8 and 687.9).

**RUNNING**

Running problems are typically caused by an overuse injury related to muscle imbalance; a minor skeletal deformity; repetitive overload
trauma; or poor flexibility, strength, endurance, or proprioception. With each step while running, the foot impact ranges from 3-8 times the athlete's body weight. Errors in training, including increasing the distance or intensity of workouts too rapidly, often result in injury to the runner. Minor variations (e.g., malalignment) in anatomy that do not cause problems at rest can predispose to injury at specific sites, such as overpronation, contributing to increased patellofemoral stress. Muscle fatigue, environmental temperature (see Chapter 690), and running surface (grass vs unyielding concrete) also contribute to injury. Prevention of injuries is possible by muscle-strengthening exercises, incorporating periods of rest into training plans, and the use of good-quality running shoes that match an athlete's foot type. Those who overpronate may benefit from a motion control shoe for maximal rearfoot and arch support. Those who mildly overpronate should utilize a stability shoe that combines extra support in the medial midsole with midsole cushion. Those who supinate should wear a neutral, cushioned shoe with increased shock absorption in the midsole and less arch support.

**Stress fractures** of all bones of the lower extremities can occur in runners (see Chapter 683.4). They have been documented at the femoral neck, inferior pubic rami, subtrochanteric area, proximal femoral shaft, proximalibia, fibula, navicular, metatarsals, desmoid. and calcaneal apophysitis. The most common are in the metatarsals, tibia, and fibula. The anterior proximal tibia, femoral neck, and tarsal navicular are most at risk for nonunion. Muscle strains most frequently affect the hamstrings, followed by the quadriceps, hip adductors, soleus, and gastronomies muscles. Tendinosis is most common in the Achilles tendon, followed by the posterior tibial, peroneal, illopoas, and proximal hamstrings. Achilles tendinosis characterized by tenderness and crepitation if acute and nodularity if chronic, initially might get better when running, and must be distinguished from retrocalcaneal bursitis. Treatment includes a period of rest from running (substitute cross-training), a heel lift, Achilles tendon stretching, and NSAIDs.

Knee pain in the runner is frequently anterior in location and commonly caused by patellofemoral stress syndrome (runner's knee), which results from excessive dynamic, usually lateral, motion of the patella in relationship to the femoral intracondylar groove (see Chapter 687.6). The athlete's body habitus (i.e., increased Q-angle, overpronation) and presence of core weakness may contribute to this overuse injury. Posterior knee pain can be caused by gastrocnemius strain, while posteromedial pain may be caused by proximal tibial stress fracture or semimembranosus/semitendinosus tendinosis. Lateral knee pain is commonly caused by iliotibial band syndrome and less so by popliteal tendinosis. Iliotibial band syndrome may combine both a component of bursitis and tendinosis owing to mechanical friction of the iliotibial band (an extension of the tensor fasciae latae) over the lateral femoral epicondyly. Treatment for knee pain in the runner includes relative rest from running, ice, and stretching of the quadriceps, hamstrings, and, in some cases, the iliotibial band. Strengthening exercises should include the quadriceps, hips, and core muscles. Foot orthotics may be indicated if there is no improvement with this treatment plan.

**Shin splints**, or medial tibial stress syndrome, is a descriptive term for pain located diffusely over the distal medial tibia and should be distinguished from tibia stress fracture and chronic compartment syndrome. Medial tibial stress syndrome often occurs in new runners with overpronation, or runners that have markedly increased their training duration in a short period of time. See Chapter 687.7 for prevention, diagnosis, and treatment.

Chronic compartment syndromes involve any of the muscle compartments with the most common being anterior. There is typically poorly localized throbbing pain that onsets 10-15 min into a run. Pain typically prevents further training limiting the risk of nerve injury. Physical exam is usually normal. Diagnosis is made by measurement of intracompartamental pressures at rest or during exercise.

**Plantar fasciitis** is an inflammation of the supporting structures of the longitudinal arch, due to repetitive cyclic loading with foot strike. Pain is typically worst with the first step out of bed in the morning and with running and is located on the medial aspect of the heel. Pes planus and overpronation are common in these patients. Treatment includes relative rest, ice, heel cord stretching, transverse friction massage, proper shoes, use of a posterior night splint, and corticosteroid injection. Therapeutic ultrasound by a trained physical therapist can be helpful in stretching the deep plantar fascia pre-friction massage in certain individuals. Calcaneal stress fracture should be considered, especially in the amenorrheic distance runner (see Chapter 691).

**SOCCER**

Injuries in soccer include any of the running injuries previously noted as well as abrasions, contusions, muscle strains, and ligament sprains (ankle, knee predominantly), partly from body-to-body contact, falls, running, and kicking. Hip problems include the hip pointer (iliac crest contusion), iliac crest apophysitis, and chronic groin pain (muscle strain, hernia, oseitis pubis). Femoral neck stress fractures, slipped femoral capital epiphysis, and avulsion fractures of the pelvis or femur should also be considered in the differential despite being uncommon (see Chapter 687.5). In general, most other upper- and lower-extremity injuries can occur in soccer.

**Traumatic brain injury** (see the discussion of concussions in Chapter 688) is common in soccer because of contact between players, player and goal post, and player and ground. The American Academy of Pediatrics recommends that youth soccer participants minimize heading the ball until more is known about the risks in young children. Proper heading technique is vital and should be taught in youth soccer. Additional points of play to consider include: On long kicks, the receiving player should trap the ball with the chest or leg, not strike it with the head; players should kick the ball about 5 ft in front of their teammates so that the latter have to come to the ball and trap with their legs; players avoid heading the ball backward toward the goal (with cervical extension); referees, as with all sports, have to keep the game under control and penalize dangerous play; and guidelines for returning to play after a concussion should be followed.

**TENNIS**

Tennis injuries occur twice as often in the lower extremity compared to the upper extremity with overall injury rates similar for boys and girls. Common areas of injury include the muscles, tendons, and ligaments of the ankle, thigh, elbow, shoulder, back, wrist, and abdomen. The risk of injury is increased by increased training duration and intensity; anatomic considerations (muscle imbalance, malalignment); poorly rehabilitated injuries with resultant deficits in flexibility and strength; and poor technique. Injuries can also be related to improper equipment, such as a racquet that is too big, or trying to learn techniques, such as hitting with top spin or with power before proper coordination and technique have been established.

Acute injuries include ankle sprains, abdominal or extreemum muscle strains, and knee sprains. Overuse injuries involve both the upper and lower extremities as well as the back. Lower-extremity injuries are related to the frequent directional changes inherent in the sport, creating significant concentric and eccentric loads on the lower extremities. These include patellofemoral stress syndrome, proximal tibial stress fractures, traction apophysitis of the calcaneus (Sever disease), and tibial tubercle (Osgood-Schlatter disease) (see Chapters 687.6 and 687.7).

In the upper extremities, overuse injuries include stress fractures of the humerus, ulna, and metacarpals, as well as traction apophysitis at the medial humeral epicondyle. The marked and rapid load and directional change associated with serving in tennis contributes to injuries of the back.

**Tennis elbow**, or lateral epicondylitis, is from repetitive overload of the wrist extensor-supinator mechanism, especially the extensor carpi radialis brevis (see Chapter 687.3). Medial epicondylitis is caused by repetitive overload of the wrist flexor-pronator muscle groups. This can secondarily involve the ulnar collateral ligament at the elbow. In young athletes, medial epicondylar apophysitis may also be associated with ulnar nerve dysfunction in the presence of an avulsion injury.
Olecranon apophysitis is similar to Osgood-Schlatter disease and is marked by pain at the olecranon with elbow extension.

At the shoulder (see Chapter 687.2), rotator cuff tendinosis is caused by repetitive overuse and may be related to anteroposterior glenohumeral instability. Subluxation of the glenohumeral joint may also be present. Biceps tendinosis can present as anterior shoulder pain. Wrist problems include an enlarged dorsal ganglion cyst, radiocarpal joint capsular (impingement) synovitis, chronic degenerative tears of the triangular fibrocartilage complex, and acute fracture of the hook of the hamate.

Basic treatment includes relative rest, ice, NSAIDs, rehabilitation, learning proper mechanics, use of properly sized racquets, counterforce bracing (elbow, wrist), forearm straps, strengthening exercises, and gradual return to tennis. Corticosteroid injections in the wrist extensor–supinator muscle group for tennis elbow are not recommended as outcomes at 1 yr are poorer than those treated with rehabilitation.

**SKATING AND SNOWBOARDING**

Injuries are related to falls (concussions, contusions, lacerations), and ski-specific mechanisms. Overall injuries have declined, partly because of better equipment (boots, bindings, poles) and slope conditions. It is strongly advised that children, adolescents, and adults wear helmets for skiing and snowboarding. Wrist protectors are also recommended for snowboarders. Injury patterns differ between these two sports with lower extremity injuries more commonly associated with skiing. Upper-extremity injuries (often from falls onto an outstretched arm) are more common in snowboarding related to the fact that both of the snowboarder's feet are strapped onto the same board reducing torque at the knees. The upper extremities, not poles, are used for balance in snowboarding putting them at increased risk.

**Skier's thumb**, a sprain of the ulnar collateral ligament of the thumb, often results from a fall with the thumb in abduction and hyperextension. Complete tears with a 45 degree joint opening require surgical intervention. Smaller degrees of joint opening can be treated with immobilization in a thumb spica cast × 4 wk. Care should be taken to rule out a concomitant Salter-Harris III fracture, which would require open reduction and internal fixation if the epiphyseal fracture is displaced. In snowboarding, shoulder dislocation, acromioclavicular joint sprain, and fractures of the wrist or collarbone are common injuries.

Lower-extremity injuries include fractures (often spiral) of the tibia ("boot top") and sprains of the high ankle and anterior cruciate ligament, the latter may include tibial eminence fracture. Hemarthrosis is present in fractures and anterior cruciate ligament injuries. Treatment is described in Chapter 683.4.

**CHEERLEADING**

Cheerleading injuries are mostly related to the gymnastic component of the sport, primarily stunting, tumbling, and pyramids. Sprains and strains comprise the majority of these injuries followed by fractures and contusions. These injuries involve the upper and lower extremities nearly equally, with the ankle being the most commonly injured joint followed by the head, neck, knee, and lower back. The use of impact-absorbing surfaces for practices reduces the risk of serious injury from falls. Ankle sprains in cheerleading predominantly involve the lateral ligaments with the ankle injured when forced into excessive plantarflexion and inversion during landings.

Similar to gymnasts, the excessive amount of repetitive hyperextension, flexion, rotation, and axial loading of the spine associated with stunting and tumbling maneuvers results in significant stress being placed upon the lower back. Another common mechanism of injury involves the act of spotting or basing another cheerleader during partner or group stunts. This involves the lifting or throwing of a teammate above the level of one's head, followed by catching them upon their descent. Injuries with this activity include sprains and strains to the upper and lower back, contributed to by poor technique, requiring coaching to avoid excessive lordosis and encourage lifting with one's legs. Concussions (brain injury) are not uncommon in cheerleading, primarily due to falls while stunting or from a pyramid. This
Bibliography


The skeletal dysplasias, bone dysplasias, and osteochondrodysplasias are a genetically and clinically heterogeneous group of disorders of skeletal development and growth with an estimated prevalence of 1 in 4,000 births. They can be divided into the osteodysplasias typified by osteogenesis imperfecta (see Chapter 701) and the chondrodysplasias. The latter result from mutations of genes that are essential for skeletal development and growth. The clinical picture is dominated by skeletal abnormalities. The manifestations may be restricted to the skeleton, but in most cases nonskeletal tissues are also involved. The disorders range in severity from lethal in utero to such mild features as to go undetected.

The chondrodysplasias are distinguished from other forms of short stature by a disproportionality of skeletal manifestations. Figure 694-1 notes the importance of cartilage in bone formation. There are 2 basic categories: predominantly with short limbs and predominantly with short trunks. Efforts to define the extent of clinical heterogeneity resulted in the delineation of well over 100 distinct entities. Many of these disorders result from mutations of a relatively small group of genes, the chondrodysplasia genes. An International Working Group on
Bone Dysplasias has named and classified these disorders into groups based on genetic cause if known or on similarities of clinical and radiographic manifestations, which often imply a common pathogenesis and a common genetic basis, if the cause is unknown (Table 694-1). The better-defined chondrodysplasia groups, such as the achondroplasia and type II collagenopathy groups, contain graded series of disorders that range from very severe to very mild. This may be true for other groups as more mutations are found and the full spectrum of clinical phenotypes associated with mutations of a given gene is defined. These disorders are clinical phenotypes distributed along spectra of phenotypic abnormality associated with mutations of particular genes. For mutations of some genes, such as COL2A1, the distribution is fairly continuous, with clinical phenotypes merging into one another across a broad range. There is much less clinical overlap for mutations of some other genes, such as FGF3, in which the distribution is discontinuous. Because most clinicians and most reference materials refer to the disorders as distinct entities, this vernacular continues to be used.

Most chondrodysplasias require the analysis of information from the history, physical examination, skeletal radiographs, family history, and laboratory testing to make a diagnosis. The process involves recognizing complex patterns that are characteristic of the different disorders (Tables 694-2, 694-3, 694-4, and 694-5). Comprehensive descriptions of disorders and references are at the Online Mendelian Inheritance in Man (OMIM) Internet site (http://omim.org/about).

**Clinical Manifestations**

**Growth**

The hallmark of the chondrodysplasias is disproportionate short stature. Although this refers to a disproportion between the limbs and the trunk, most disorders exhibit some shortening of both, and subtle degrees of disproportion may be difficult to appreciate, especially in premature, obese, or edematous infants. Disproportionate shortening of the limbs should be suspected if the upper limbs do not reach the mid pelvis in infancy or the upper thigh after infancy. Disproportionate shortening of the trunk is indicated by a short neck, small chest, and protuberant abdomen. Skeletal disproportion is usually accompanied by short stature (length and height below the 3rd percentile); these measurements are occasionally within the low-normal range early in the course of certain conditions. There may also be disproportionate shortening of different segments of the limbs; the particular pattern can provide clues for specific diagnoses. Shortening is greatest in the proximal segments (upper arms and legs) in achondroplasia; this is termed rhizomelic shortening. Disproportionate shortening of the middle segments (forearms and lower legs) is called mesomelic shortening; acromelic shortening involves the hands and feet.

With some exceptions, there is a strong correlation between the age at onset and the clinical severity. Many of the lethal neonatal chondrodysplasias are evident during routine fetal ultrasound examinations performed at the end of the 1st trimester of gestation (see Table 694-4). Gestational standards exist for long-bone lengths; discrepancies are often detected between biparietal diameter of the skull and long-bone lengths. Many disorders become apparent around the time of birth; others manifest during the 1st yr of life. A number of disorders manifest in early childhood and a few in late childhood or later.

**Non-Growth-Related Manifestations**

Most patients also have problems unrelated to growth. Skeletal deformities, such as abnormal joint mobility, protuberances at and around joints, and angular deformities, are common and usually symmetric. Skeletal abnormalities can adversely affect nonskeletal tissues. Impaired growth at the base of the skull and of vertebral pedicles reduces the size of the spinal canal in achondroplasia and can contribute to spinal cord compression. Short ribs reduce thoracic volume, which can compromise breathing in patients with short trunk chondrodysplasias. Cleft palate (see Chapter 310) is common to many disorders, presumably reflecting defective palatal growth.

Manifestations may be unrelated to the skeleton; they reflect expression of mutant genes in nonskeletal tissues. Examples include retinal detachment in spondyloepiphyseal dysplasia congenita, sex reversal in campomelic dysplasia, congenital heart malformations in Ellis-van Creveld syndrome, immunodeficiency in cartilage-hair hypoplasia, and renal dysfunction in asphyxiating thoracic dystrophy. These non-skeletal problems provide valuable clues to specific diagnoses and must be managed clinically (see Table 694-3).

**Family and Reproductive History**

A family history might identify relatives with the condition; a mendelian inheritance pattern may be elicited. Because the presentation can vary in some disorders, features that might be related to the disorder should be identified. Special attention should be given to mild degrees of short stature, disproportion, deformities, and other manifestations such as precocious osteoarthritis because they may be overlooked. Physical examination of relatives may be useful, as may the review of their photographs, radiographs, and medical and laboratory records.

A reproductive history might reveal previous stillbirths, fetal losses, and other abnormal pregnancy outcomes resulting from a skeletal dysplasia. Pregnancy complications, such as polyhydramnios or reduced fetal movement, are common in bone dysplasias, especially neonatal lethal variants.

Even though most of the skeletal dysplasias are genetic, it is common to have no family history of the disorder. New mutations are common for autosomal dominant disorders, especially lethal disorders in the perinatal period (thanatophoric dysplasia, osteogenesis imperfecta). Most cases of achondroplasia result from new mutations. Germ cell mosaicism, in which a parent has clones of mutant germ cells, has been observed in osteogenesis imperfecta and in other dominant disorders. A negative family history is usually seen in recessive disorders. Few of these conditions are caused by X-linked mutations. Prenatal diagnosis is available for disorders that have a genetic locus identified. Appropriateness of the testing depends on many factors, and genetic counseling is warranted for these families.

**Radiographic Features**

Radiographic evaluation for a chondrodysplasia should include plain films of the entire skeleton. Efforts should be made to identify which bones and which parts of bones (epiphyses, metaphyses, diaphyses) are most affected. If possible, films taken at different ages should be examined because the radiographic changes evolve with time. Films taken before puberty are generally more informative because pubertal closure of the epiphyses obliterates many of the signs needed for a radiographic diagnosis. Prenatal diagnosis may also be possible with fetal ultrasound.

**Diagnosis**

If an infant or child is short with disproportionate features, a diagnosis is established by matching the observed clinical picture (defined
<table>
<thead>
<tr>
<th>GENE</th>
<th>CHROMOSOME</th>
<th>LOCATION</th>
<th>PROTEIN FUNCTION</th>
<th>CLINICAL PHENOTYPE</th>
<th>DISEASE MECHANISM</th>
<th>INHERITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL2A1</td>
<td>12q13.1-q13.3</td>
<td>Cartilage matrix protein Alpha 1 chain</td>
<td>Achondrogenesis II, Hypochondrogenesis</td>
<td>200610 Dominant negative AD*</td>
<td>Dominant negative AD*</td>
<td>AD*</td>
</tr>
<tr>
<td>COL11A1</td>
<td>1p21</td>
<td>Cartilage matrix protein Alpha 1 chain</td>
<td>Stickler-like dysplasia</td>
<td>184840 Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>COL11A2</td>
<td>6q21-21.3</td>
<td>Cartilage matrix protein Alpha 2 chain</td>
<td>Stickler-like dysplasia</td>
<td>184840 Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>COL9A2</td>
<td>1p32.2-p33</td>
<td>Type IX collagen Alpha 2 chain</td>
<td>MED 600969</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>COL9A3</td>
<td>20q13.33</td>
<td>Type IX collagen Alpha 3 chain</td>
<td>MED 600969</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>COL10A1</td>
<td>6p21-q22</td>
<td>Cartilage matrix protein Alpha 1 chain</td>
<td>Stickler-like dysplasia</td>
<td>184840 Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>SOX9</td>
<td>17q11.2-q21</td>
<td>Transcription factor</td>
<td>114290 Haploinsufficiency AD</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>RANKL</td>
<td>1p36.2</td>
<td>Transcription factor</td>
<td>114290 Haploinsufficiency AD</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>PGKF</td>
<td>3q27-q29</td>
<td>Transcription factor</td>
<td>114290 Haploinsufficiency AD</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>RUNX2</td>
<td>11q13.5</td>
<td>Transcription factor</td>
<td>114290 Haploinsufficiency AD</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>LMX1B</td>
<td>11q13.5</td>
<td>Transcription factor</td>
<td>114290 Haploinsufficiency AD</td>
<td>Dominant negative AD</td>
<td>Dominant negative AD</td>
<td>AD</td>
</tr>
<tr>
<td>TRPV4</td>
<td>12q24.1-2q24.2</td>
<td>Transmembrane channel ion channel</td>
<td>Brachyolmia</td>
<td>1184252 Gain of function AD</td>
<td>Gain of function AD</td>
<td>AD</td>
</tr>
</tbody>
</table>

*Usually lethal.

† Also called CBFA1.

AD, autosomal dominant; AR, autosomal recessive; ATD, Jeune asphyxiating thoracic dystrophy; CHH, cartilage-hair hypoplasia; DTD, diastrophic dysplasia; FGR, fibroblast growth factor; MED, multiple epiphyseal dysplasia; MIM, multiple epiphyseal dysplasia; SED, spondyloepiphyseal dysplasia; SEMD, spondyloepimetaphyseal dysplasia; SMDK, spondylometaphyseal dysplasia Kozlowski type; SRPIII, short rib polydactyly syndrome.
Associated Anomalies in Skeletal Dysplasias

Table 694-2 Major Problems Associated with Skeletal Dysplasias

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethality*</td>
<td>Thanatophoric dysplasia</td>
</tr>
<tr>
<td>Associated anomalies†</td>
<td>Ellis-van Creveld syndrome</td>
</tr>
<tr>
<td>Short stature</td>
<td>Common to almost all</td>
</tr>
<tr>
<td>Cervical spine dislocations</td>
<td>Larsen syndrome</td>
</tr>
<tr>
<td>Severe limb bowing</td>
<td>Metaphyseal dysplasia, Schmid type</td>
</tr>
<tr>
<td>Spine curvatures</td>
<td>Metatropic dysplasia</td>
</tr>
<tr>
<td>Clubfeet</td>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Fractures</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Pneumonias, aspirations</td>
<td>Camptomelic dysplasia</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Joint problems (hips, knees)</td>
<td>Most skeletal dysplasias</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Common (greatest with cleft palate)</td>
</tr>
<tr>
<td>Myopia/cataracts</td>
<td>Stickler syndrome</td>
</tr>
<tr>
<td>Immunodeficiency†</td>
<td>Cartilage-hair hypoplasia, Schimke immunoosseous dysplasia</td>
</tr>
<tr>
<td>Poor body image</td>
<td>Variable, but common to all</td>
</tr>
<tr>
<td>Sex reversal</td>
<td>Camptomelic dysplasia</td>
</tr>
</tbody>
</table>

*Mostly a result of severely reduced size of thorax.
†See Table 694-3.
‡At least 4 additional disorders, all involving the metaphyses, can have immunodeficiency.

Molecular genetic testing for chondrodysplasias is very useful, especially for disorders in which recurrent mutations occur (typical achondroplasia has the same FGFR3 mutation). Mutation testing for achondroplasia is available, although the diagnosis is usually made clinically. The greatest utility for testing may be for prenatal testing for couples where both parents have typical (heterozygous) achondroplasia. Their children are at a 25% risk of the much more severe homozygous achondroplasia, which can be detected by mutation analysis. Preimplantation genetic testing can be used to identify double dominant mutations. Another example of testing is in disorders resulting from mutations of DTDST. These disorders are inherited in an autosomal recessive manner, and a limited number of mutant alleles have been found. If the mutations are identified in the patient, they should be detectable in the parents and potentially used for prenatal diagnosis. Mutational analysis is now commercially available for many of the skeletal dysplasias and is increasingly used to confirm clinical diagnosis and for future pregnancy planning.

Many of the chondrodysplasias have distinct histologic changes of the skeletal growth plate. Sometimes such tissues obtained at biopsy or discarded from a surgical procedure are helpful diagnostically. It is uncommon to make a diagnosis histologically if it was not already suspected on clinical or radiographic grounds.

Table 694-3 Associated Anomalies in Skeletal Dysplasias

<table>
<thead>
<tr>
<th>ANOMALY</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart defects</td>
<td>Ellis-van Creveld syndrome, Jeune syndrome</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>Short rib polydactyly, Majewski type</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Ear cysts</td>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Encephalocoele</td>
<td>Dyssegmental dysplasia</td>
</tr>
<tr>
<td>Hemivertebrae</td>
<td>Dyssegmental dysplasia</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>Camptomelic dysplasia</td>
</tr>
<tr>
<td>Nail dysplasia</td>
<td>Ellis-van Creveld syndrome</td>
</tr>
<tr>
<td>Conical teeth, oligodontia</td>
<td>Ellis-van Creveld syndrome</td>
</tr>
<tr>
<td>Multiple oral frenula</td>
<td>Ellis-van Creveld syndrome</td>
</tr>
<tr>
<td>Dentinogenesis imperfecta</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Pretibial skin dimples</td>
<td>Camptomelic dysplasia</td>
</tr>
<tr>
<td>Cataracts, retinal detachment</td>
<td>Stickler syndrome</td>
</tr>
<tr>
<td>Intestinal atresia</td>
<td>Saldino-Noonan</td>
</tr>
<tr>
<td>Renal cysts</td>
<td>Saldino-Noonan</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>Thanatophoric dysplasia</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>Chondrodysostia punctata</td>
</tr>
<tr>
<td>Hitchhiker thumb</td>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Sparse scalp hair</td>
<td>Cartilage-hair hypoplasia</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>Robinow syndrome</td>
</tr>
<tr>
<td>Hypoplastic nasal bridge</td>
<td>Acrodyostosis</td>
</tr>
<tr>
<td>Clavicular agenesis</td>
<td>Cleidocranial dysplasia</td>
</tr>
<tr>
<td>Genital hypoplasia</td>
<td>Robinow syndrome</td>
</tr>
<tr>
<td>Tail</td>
<td>Metatropic dysplasia</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>Beemer-Langer syndrome</td>
</tr>
<tr>
<td>Blue sclera</td>
<td>Osteogenesis imperfecta</td>
</tr>
</tbody>
</table>

Table 694-4 Lethal Neonatal Dwarfism

<table>
<thead>
<tr>
<th>USUALLY FATAL*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondrogenesis (different types)</td>
<td>Thanatophoric dysplasia</td>
</tr>
<tr>
<td>Short rib polydactyly (different types)</td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Homozygous achondroplasia</td>
<td>Camptomelic dysplasia</td>
</tr>
<tr>
<td>Dyssegmental dysplasia, Silverman-Handmaker type</td>
<td>Osteogenesis imperfecta, type II</td>
</tr>
<tr>
<td>Hypophosphatasia (congenital form)</td>
<td>Chondrodysplasia punctata (rhizomelic form)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OFTEN FATAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asphyxiating thoracic dystrophy (Jeune syndrome)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OCCASIONALLY FATAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis-van Creveld syndrome</td>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Metatropic dwarfism</td>
<td>Kniest dysplasia</td>
</tr>
</tbody>
</table>

*A few prolonged survivors have been reported in most of these disorders.
Usually Nonlethal Dwarfing Conditions Recognizable at Birth or Within 1st Few Mo of Life

<table>
<thead>
<tr>
<th>MOST COMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Osteogenesis imperfecta (types I, III, IV)</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia congenita</td>
</tr>
<tr>
<td>Diastrophic dysplasia</td>
</tr>
<tr>
<td>Ellis-van Creveld syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LESS COMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrodysplasia punctata (some forms)</td>
</tr>
<tr>
<td>Kniest dysplasia</td>
</tr>
<tr>
<td>Langer mesomelic dysplasia</td>
</tr>
</tbody>
</table>

**MOLECULAR GENETICS**

A number of chondrodysplasia genes have been identified (see Table 694-1). They encode several categories of proteins, including cartilage matrix proteins, transmembrane receptors, ion transporters, and transcription factors. The number of identified gene loci is smaller than anticipated from the number of recognized clinical phenotypes. The majority of patients have disorders that map to fewer than 10 loci; mutations at 2 loci (COL2A1 and FGFR3) account for more than half of all cases. There may be a limited number of genes whose function is critical to skeletal development, especially linear bone growth; mutations in these genes give rise to a wide range of chondrodysplasia clinical phenotypes. New genes harboring mutations that cause chondrodysplasias continue to be identified with advances in detection technology.

Mutations at the COL2A1 and FGFR3 loci illustrate different genetic characteristics. COL2A1 mutations are distributed throughout the gene, with few instances of recurrence in unrelated persons. In contrast, FGFR3 mutations are restricted to a few locations within the gene, and occurrence of new mutations at these sites in unrelated persons is the rule. There is a strong correlation between clinical phenotype and mutation site for FGFR3, but not COL2A1, mutations.

**PATHOPHYSIOLOGY**

Chondrodysplasia mutations act through different mechanisms. Most mutations involving cartilage matrix proteins cause disease when only 1 of the 2 copies (alleles) of the relevant gene is mutated. These mutations usually act through a dominant negative mechanism in which the protein products of the mutant allele interfere with the assembly and function of multimeric molecules that contain the protein products of both the normal and mutant alleles. The type II collagen molecule is a triple helix composed of 3 collagen chains, which are the products of the type II collagen gene COL2A1. When chains from both normal and mutant alleles are combined to form triple helices, most molecules contain at least 1 mutant chain. It is not known how many mutant chains are required to produce a dysfunctional molecule but, depending on the mutation, it theoretically could be as few as 1.

Mutations involving type X collagen differ from the model just described. They map to the region of the chain that is responsible for chain recognition; the chains must recognize each other before they can assemble into collagen molecules. Mutations are thought to disrupt this process. As a result, none of the mutant chains is incorporated into molecules. This mechanism is haploinsufficiency because the products of the mutant allele are functionally absent and the normal allele is insufficient for normal function. Mutations involving ion transport genes also act through a loss of function of the transporters. Mutations of transmembrane receptors studied to date appear to act through a gain of function; the mutant receptors initiate signals in a constitutive manner independent of their normal ligands.

Regardless of genetic mechanism, the mutations ultimately disrupt endochondral ossification, the biologic process responsible for the development and linear growth of the skeleton (see Fig. 694-1). Indeed, a wide range of morphologic abnormalities of the skeletal growth plate, the anatomic structure in which endochondral ossification occurs, have been described in the chondrodysplasias.

**TREATMENT**

The first step is to establish the correct diagnosis. This allows one to predict a prognosis and to anticipate the medical and surgical problems associated with a particular disorder. Establishing a diagnosis helps to distinguish between lethal disorders and nonlethal disorders in a prenatally or neonatal infant (see Tables 694-4 and 694-5). A poor prognosis for long-term survival might argue against initiating extreme lifesaving measures for thanatophoric dysplasia or achondrogenesis types Ib or II, whereas such measures may be indicated for infants with spondyloepiphyseal dysplasia congenita or diastrophic dysplasia, which have a good prognosis if the infant survives the newborn period.

Because there is no definitive therapy to normalize bone growth in any of the disorders, management is directed at preventing and correcting skeletal deformities, treating nonskeletal complications, providing genetic counseling, and helping patients and families learn to cope. Each disorder has its own unique set of problems, and consequently management must be tailored to each disorder.

There are a number of problems common to many chondrodysplasias for which general recommendations can be made. Children with most chondrodysplasias should avoid contact sports and other activities that cause injury or stress to joints. Good dietary habits should be established in childhood to prevent or minimize obesity in adulthood. Dental care should be started early to minimize crowding and malalignment of teeth. Children and relatives should be given the opportunity to participate in support groups, such as the Little People of America (http://www.lpoaonline.org) and Human Growth Foundation (http://www.hgfound.org).

Two controversial approaches have been used to increase bone length. Surgical limb lengthening has been employed for a few disorders. Its greatest success has been in achondroplasia in which nonskeletal tissues tend to be redundant and easily stretched. The procedure is usually performed during adolescence. Pharmacologic doses of human growth hormone comparable to those used to treat Turner syndrome have also been tried in several disorders; the results have been equivocal. Animal studies suggest that C-type natriuretic peptide may promote linear bone growth in achondroplasia. Clinical trials are beginning to test the efficacy of this approach.

Bibliography is available at Expert Consult.
Bibliography
Disorders of cartilage matrix proteins resulting in bone and joint disorders can be classified in 5 categories corresponding to the defective proteins: 3 collagens and the noncollagenous proteins COMP (cartilage oligomeric matrix protein), matrilin 3, and aggrecan. The clinical phenotypes and clinical severity differ between and within the groups, especially the spondyloepiphysyeal dysplasia (SED) group.
Bone and Joint Disorders

Part XXXII

◆

Figure 695-1 Spondyloepiphyseal dysplasia congenita is shown in infancy (A) and early childhood (B, C). Note the short extremities, relatively normal hands, flat facies, and exaggerated lordosis.

SPONDYLOEPPHYSEAL DYSPLASIAS

The term spondyloepiphyseal dysplasia refers to a heterogeneous group of disorders characterized by shortening of the trunk and, to a lesser extent, the limbs. Severity ranges from achondrogenesis type II to the slightly less-severe hypochondrogenesis (although both types are lethal in the perinatal period) to SED congenita and its variants, including Kniest dysplasia (which is apparent at birth and is usually nonlethal), to late-onset SED (which might not be detected until adolescence or later). The radiographic hallmarks are abnormal development of the vertebral bodies and of epiphyses, the extent of which corresponds to the clinical severity. Most of the SEDs result from heterozygous mutations of COL2A1; they are autosomal dominant disorders. The mutations are dispersed throughout the gene; there is a poor correlation between the mutation’s location and the resultant clinical phenotype. For familial cases, prenatal diagnosis is possible if the mutation is identified. Schimke immuno-osseous dysplasia may be an exception because it is an autosomal recessive disorder characterized by short stature, hyperpigmented macules, unusual facies, proteinuria and progressive renal failure, cerebral ischemia, and a T-cell defect with lymphopenia and recurrent infections.

Lethal Spondyloepiphyseal Dysplasias

Achondrogenesis type II (MIM 200610) is characterized by severe shortening of the neck and trunk and especially the limbs and by a large, soft head. Fetal hydrops and prematurity are common; infants are stillborn or die shortly after birth. Hypochondrogenesis (MIM 200610) refers to a clinical phenotype intermediate between achondrogenesis type II and SED congenita. It is typically lethal in the newborn period.

The severity of radiographic changes correlates with the clinical severity. Both conditions produce short, broad tubular bones with cupped metaphyses. The pelvic bones are hypoplastic, and the cranial bones are not well mineralized. The vertebral bodies are poorly ossified in the entire spine in achondrogenesis type II and in the cervical and sacral spine in hypochondrogenesis. The pedicles are ossified in both.

Spondyloepiphyseal Dysplasia Congenita

The phenotype of this group, SED congenita (MIM 183900), is apparent at birth. The head and face are usually normal, but a cleft palate is common. The neck is short and the chest is barrel shaped (Fig. 695-1). Kyphosis and exaggeration of the normal lumbar lordosis are common. The proximal segments of the limbs are shorter than the hands and feet, which often appear normal. Some infants have clubfoot or exhibit hypotonia.

Skeletal radiographs of the newborn reveal short tubular bones, delayed ossification of vertebral bodies, and proximal limb bone epiphyses (Fig. 695-2). Hypoplasia of the odontoid process, a short, square pelvis with a poorly ossified symphysis pubis, and mild irregularity of metaphyses are apparent.

Infants usually have normal developmental milestones; a waddling gait typically appears in early childhood. Childhood complications include respiratory compromise from spinal deformities and spinal cord compression because of cervicomedullary instability. The disproportionate and shortening become progressively worse with age, and adult heights range from 95–128 cm. Myopia is typical; adults are predisposed to retinal detachment. Precocious osteoarthritis occurs in adulthood and requires surgical joint replacement.

KNIEST DYSPLASIA

The Kniest dysplasia variant of SED (MIM 156550) manifests at birth with a short trunk and limbs associated with a flat face, prominent eyes, enlarged joints, cleft palate, and clubfoot (Fig. 695-3). Radiographs show vertebral defects and short tubular bones with epiphyseal irregularities and metaphyseal enlargement that gives rise to a dumbbell appearance.

Motor development is often delayed because of the joint deformities, although intelligence is normal. Hearing loss and myopia commonly develop during childhood, and retinal detachment can occur as a late complication. Joint enlargement progresses during childhood and becomes painful; it is accompanied by flexion contractures and muscle atrophy, which may be incapacitating by adolescence.
LATE-ONSET SPONDYLOEPIPHYSEAL DYSPLASIA

Late-onset SED is a mild to very mild clinical phenotype characterized by slightly short stature associated with mild epiphyseal and vertebral abnormalities on radiographs. It is typically detected during childhood or adolescence but can go unrecognized until adulthood when precocious osteoarthritis appears. This designation is nosologically distinct from SED tarda, which is clinically similar but results from mutation of the X-linked gene SEDL.

AGGREGAN-RELATED SPONDYLOEPIPHYSEAL DYSPLASIAS

Mutations of aggrecan have been detected in 2 SED-like conditions. SED-Kimberley (MIM 608361) is relatively mild, with short stature, stocky build, and early onset osteoarthritis of weightbearing joints. A more severe and generalized clinical phenotype with characteristic radiographic changes including widened metaphyses is observed in spondyloepimetaphyseal dysplasia–Aggrecan type (MIM 612813).

STICKLER SYNDROME/DYSPLASIA (HEREDITARY OSTEOARTHOPTHALMOPATHY)

Short stature is not a feature of Stickler dysplasia (MIM 184840). It resembles SED because of its joint and eye manifestations. Mutations of genes encoding type II (COL2A1), type XI (COL11A1, COL11A2), and type IX (COL9A1) collagens have been identified in Stickler-like disorders (MIM 184840, MIM 215150). Stickler dysplasia is often identified in the newborn because of cleft palate and micrognathia (Pierre Robin anomaly; see Chapter 311). Twenty-five percent of patients with Stickler syndrome have Pierre Robin anomaly; 30% of patients with Pierre Robin anomaly have Stickler syndrome. Infants typically have severe myopia and additional ophthalmologic complications, including choroidoretinal and vitreous degeneration; retinal detachment is common during childhood (Fig. 695-4). Sensorineural hearing loss can arise during adolescence, which is when symptoms of significant osteoarthritis can also begin. Special attention must be given to the eye complications even in childhood. Osteoarticular manifestations include joint hypermobility (especially hip), muscle hypotonia, metaphyseal–epiphyseal dysplasia; progressive osteoarthritis of spine and peripheral joints, which may require hip replacement surgery before age 30 yr and decreased bone density. Similar manifestations may be seen in other diseases with mutations in type II and XI collagen genes (Table 695-1).

<table>
<thead>
<tr>
<th>Table 695-1</th>
<th>Other Genetic Diseases Associated with Mutations in Type II and Type XI Collagen Genes, with Clinical Presentations Similar to That of Stickler Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypes associated with COL2A1 mutations</td>
<td>Achondrogenesis type 2 Hypochondrogenesis Spondyloepiphyseal dysplasia congenita Spondyloepimetaphyseal dysplasia, Strudwick type Kniest dysplasia Dysplasia with altered vertebral contours Some of the juvenile joint diseases Phenotypes associated with COL11A1 mutations Marshall syndrome Phenotypes associated with COL11A2 mutations Otoospondylometaphyseal dysplasia Weissenbach-Zweymuller syndrome Some cases of isolated sensorineural deafness</td>
</tr>
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</table>

From Couchouron T, Masson C: Early-onset progressive osteoarthritis with hereditary progressive ophthalmology or Stickler syndrome. Joint Bone Spine 78(4):49, 2011, Table 1, p. 48.
Bone and Joint Disorders

The mutations are heterozygous in both; they are autosomal dominant traits. The clinical phenotypes are restricted to skeletal tissues.

Newborns with pseudoachondroplasia are average in size and appearance. Gait abnormalities and short stature mainly affect the limbs and become apparent in late infancy. The short stature becomes marked as the child grows and is associated with generalized joint laxity (Fig. 695-7). The hands are short, broad, and deviated in an ulnar direction; the forearms are bowed. Developmental milestones and intelligence are usually normal. Lumbar lordosis and deformities of the knee develop during childhood; the latter often requires surgical correction. Pain is common in weightbearing joints during childhood and adolescence, and osteoarthritis develops late in the 2nd decade of life. Adults range in height from 105-128 cm.

Skeletal radiographs show distinctive abnormalities of vertebral bodies and of both epiphyses and metaphyses of tubular bones (Fig. 695-8).

Figure 695-4 Face and profile of the daughter with Stickler syndrome type I. Note the flat nasal bridge, the mild epicanthal folds and discrete micrognathia. Face and profile of the mother with Stickler syndrome type I. The mother shows at first sight no clear facial characteristics of Stickler syndrome. (From Baijens LWJ, De Leenheer EMR, Weekamp HH, et al: Stickler syndrome type I and Stapes ankylosis. Int J Pediatr Otorhinolaryngol 68:1573–1580, 2004, Fig. 2.)

Schmid metaphyseal dysplasia (MIM 156500) is one of several chondrodysplasias in which metaphyseal abnormalities dominate the radiographic features. It typically manifests in early childhood with mild short stature, bowing of the legs, and a waddling gait (Fig. 695-5). Joints, such as the wrist, may be enlarged. Radiographs show flaring and irregular mineralization of the metaphyses of tubular bones of the proximal limbs (Fig. 695-6). Coxa vara is usually present and can require surgical correction. Short stature becomes more evident with age and affects the lower extremities more than the upper extremities; the manifestations are limited to the skeleton.

Schmid metaphyseal chondrodysplasia is caused by heterozygous mutations of the gene encoding type X collagen; it is an autosomal dominant trait. The distribution of type X collagen is restricted to the region of growing bone in which cartilage is converted into bone. This might explain why radiographic changes are confined to the metaphyses.

PSEUDOACHONDROPLASIA AND MULTIPLE EPiphySEAL DysPLASIA

Pseudoachondroplasia (MIM 177170) and multiple epiphyseal dysplasia (MED) (MIM 600969) are 2 distinct phenotypes that are grouped together because they result from mutations of the gene encoding COMP. The mutations are heterozygous in both; they are autosomal dominant traits. The clinical phenotypes are restricted to skeletal tissues.

Newborns with pseudoachondroplasia are average in size and appearance. Gait abnormalities and short stature mainly affect the limbs and become apparent in late infancy. The short stature becomes marked as the child grows and is associated with generalized joint laxity (Fig. 695-7). The hands are short, broad, and deviated in an ulnar direction; the forearms are bowed. Developmental milestones and intelligence are usually normal. Lumbar lordosis and deformities of the knee develop during childhood; the latter often requires surgical correction. Pain is common in weightbearing joints during childhood and adolescence, and osteoarthritis develops late in the 2nd decade of life. Adults range in height from 105-128 cm.

Skeletal radiographs show distinctive abnormalities of vertebral bodies and of both epiphyses and metaphyses of tubular bones (Fig. 695-8).

The MED phenotype has skeletal abnormalities that predominantly affect the epiphyses as noted on radiographs. Two classic forms are a severe Fairbank type and a mild Ribbing type. Because of overlap in clinical features and because COMP mutations are found in both types,
they may be considered clinical variants. This nomenclature is not generally used now.

The more severe clinical phenotype has its onset during childhood, with mild short-limbed short stature, pain in weightbearing joints, and a waddling gait. Radiographs show delayed and irregular ossification of epiphyses. In more mildly affected patients the disorder might not be recognized until adolescence or adulthood. Radiographic changes may be limited to the capital femoral epiphyses. In the latter case, mild MED must be distinguished from bilateral Legg-Calvé-Perthes disease (see Chapter 678.3). Precocious osteoarthritis of hips and knees is the major complication in adults with MED. Adult heights range from 136-151 cm.

There are families with clinical and radiographic manifestations of MED that are not caused by mutations of COMP. Some are linked to the gene encoding 1 of the type IX collagen chains. It has been suggested that COMP and type IX collagen interact functionally in cartilage matrix, thus explaining why mutations of different genes produce similar pictures. Mutations of the genes coding for another cartilage

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**Figure 695-5** Female patient with metaphyseal dysplasia, type Schmid. The facies are normal and stature is mildly reduced. Mild tibia vara is present.

**Figure 695-6** Radiograph of lower extremities in Schmid metaphyseal dysplasia showing short tubular bones and metaphyseal flaring and irregularities, abnormal capital femoral epiphyses, and femoral necks. The epiphyses are normal. Coxa vara is present.

**Figure 695-7 A, B** Pseudoachondroplasia in an adolescent boy. The facies and head circumference are normal. There is shortening of all extremities and bowing of the lower extremities. B, Photograph of hands, demonstrating short stubby fingers.
matrix protein, matrilin 3, and the diastrophic dysplasia sulfate transporter have also been found in patients with MED. For familial cases of pseudoachondroplasia and MED resulting from mutation in COMP, prenatal diagnosis is available.

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Heterozygous mutations of genes encoding FGFR3 (fibroblast growth factor receptor 3) and PTHR (parathyroid hormone receptor) result in disorders involving transmembrane receptors. The mutations cause the receptors to become activated in the absence of physiologic ligands, which accentuates normal receptor function of negatively regulating bone growth. The mutations act by gain of negative function. In the FGFR3 mutation group, in which the clinical phenotypes range from severe to mild, the severity appears to correlate with the extent to which the receptor is activated. PTHR and especially FGFR3 mutations tend to recur in unrelated individuals.

**ACHONDROPLASIA GROUP**

The achondroplasia group represents a substantial percentage of patients with chondrodysplasias and contains thanatophoric dysplasia (TD), the most common lethal chondrodysplasia, with a birth prevalence of 1 in 35,000 births; achondroplasia, the most common nonlethal chondrodysplasia, with a birth prevalence of 1 in 15,000 to 1 in 40,000 births; and hypochondroplasia. All 3 have mutations in a small number of locations in the FGFR3 gene. There is a strong correlation between the mutation site and the clinical phenotype.

**Thanatophoric Dysplasia**

TD (MIM 187600, 187610) manifests before or at birth. In the former situation, ultrasonographic examination in midgestation or later reveals a large head and very short limbs; the pregnancy is often accompanied by polyhydramnios and premature delivery. Very short limbs, short neck, long narrow thorax, and large head with midfacial hypoplasia dominate the clinical phenotype at birth (Fig. 696-1). The cloverleaf skull deformity known as kleeblattschädel is sometimes found. Newborns have severe respiratory distress because of their small thorax. Although this distress can be treated by intense respiratory care, the long-term prognosis is poor.

Skeletal radiographs distinguish 2 slightly different forms called TD I and TD II. In the more common TD I, radiographs show large calvariae with a small cranial base, marked thinning and flattening of vertebral bodies visualized best on lateral view, very short ribs, severe hypoplasia of pelvic bones, and very short and bowed tubular bones.
Skeletal radiographs confirm the diagnosis (see Figs. 696-3 and 696-4). Diagnosis

but occasionally plots within the low-normal range. Usually, birth length is slightly less than normal extensible, but extension is restricted at the elbow. A thoracolumbar gibbus is often found. Most joints are hyperextensible, but limitation may be greater in the knees and the fingers often display a trident configuration. Most joints are hyperextensible, but limitation may be greater in the knees and the fingers often display a trident configuration.

Achondroplasia (MIM 100800) is the prototype chondrodysplasia. It typically manifests at birth with short limbs, a long narrow trunk, and small head with midfacial hypoplasia and prominent forehead (Fig. 696-3). The limb shortening is greatest in the proximal segments, and the fingers often display a trident configuration. Most joints are hyperextensible, but extension is restricted at the elbow. A thoracolumbar gibbus is often found. Usually, birth length is slightly less than normal but occasionally plots within the low-normal range.

Achondroplasia

Achondroplasia (MIM 100800) is the prototype chondrodysplasia. It typically manifests at birth with short limbs, a long narrow trunk, and a large head with midfacial hypoplasia and prominent forehead (Fig. 696-3). The limb shortening is greatest in the proximal segments, and the fingers often display a trident configuration. Most joints are hyperextensible, but extension is restricted at the elbow. A thoracolumbar gibbus is often found. Usually, birth length is slightly less than normal but occasionally plots within the low-normal range.

Diagnosis

Skeletal radiographs confirm the diagnosis (see Figs. 696-3 and 696-4). The calvarial bones are large, whereas the cranial base and facial bones are small. The vertebral pedicles are short throughout the spine as noted on a lateral radiograph. The interpedicular distance, which normally increases from the 1st to the 5th lumbar vertebra, decreases in achondroplasia. The iliac bones are short and round, and the acetabular roofs are flat. The tubular bones are short with mildly irregular and flared metaphyses. The fibula is disproportionately long compared with the tibia.

Clinical Manifestations

Infants usually exhibit delayed motor milestones, often not walking alone until 18-24 mo. This is because of hypotonia and mechanical difficulty balancing the large head on a normal-sized trunk and short extremities. Intelligence is normal unless central nervous system complications develop. As the child begins to walk, the gibbus usually gives way to an exaggerated lumbar lordosis.

Infants and children with achondroplasia progressively fall below normal standards for length and height. They can be plotted against standards established for achondroplasia. Adult heights typically are 118-145 cm for men and 112-136 cm for women. Surgical limb lengthening and human growth hormone treatment have been used to increase height; both are controversial. C-type natriuretic peptide may stimulate bone growth in achondroplasia based on studies in animal models. Clinical studies are in the initial phases of testing.

Virtually all infants and children with achondroplasia have large heads, although only a fraction have true hydrocephalus. Head circumference should be carefully monitored using standards developed for achondroplasia, as should neurologic function in general. The spinal canal is stenotic, and spinal cord compression can occur at the foramen magnum and in the lumbar spine. The former usually occurs in infants and small children; it may be associated with hypotonia, failure to thrive, quadriplegia, central and obstructive apnea, and sudden death. Surgical correction may be required for severe stenosis. Lumbar spinal stenosis usually does not occur until early adulthood. Symptoms include paresthesias, numbness, and claudication in the legs. Loss of bladder and bowel control may be late complications.

Bowing of the legs is common and might need to be corrected surgically. Other common problems include dental crowding, articulation difficulties, obesity, and frequent episodes of otitis media, which can contribute to hearing loss.

Genetics

All patients with typical achondroplasia have mutations at FGFR3 codon 380. The mutation maps to the transmembrane domain of the receptor and is thought to stabilize receptor dimers that enhance receptor signals, the consequences of which inhibit linear bone growth. Achondroplasia behaves as an autosomal dominant trait; most cases arise from a new mutation to normal parents.

Because of the high frequency of achondroplasia among dwarving conditions, it is relatively common for adults with achondroplasia to...
Hypochondroplasia

Hypochondroplasia (MIM 146000) resembles achondroplasia but is milder. Usually, it is not apparent until childhood, when mild short stature affecting the limbs becomes evident. Children have a stocky build and slight frontal bossing of the head. Learning disabilities may be more common in this condition. Radiographic changes are mild and consistent with the mild achondroplastic phenotype. Complications are rare; in some patients the condition is never diagnosed. Adult heights range from 116–146 cm. An FGFR3 mutation at codon 540 has been found in many patients with hypochondroplasia. Genetic heterogeneity exists in hypochondroplasia; that is, SHOX mutations are associated with a very similar clinical phenotype. Recombinant growth hormone therapy may enhance growth and improve body disproportion.

Jansen metaphyseal dysplasia

Jansen metaphyseal chondrodysplasia (MIM 156400) is a rare, dominantly inherited chondrodysplasia characterized by severe shortening of limbs associated with an unusual facial appearance. Sometimes it is accompanied by clubfoot and hypercalcemia. At birth, a diagnosis can be made from these clinical findings and radiographs that show short tubular bones with characteristic metaphyseal abnormalities that include flaring, irregular mineralization, fragmentation, and widening of the physisal space. The epiphyses are normal.

The joints become enlarged and limited in mobility with age. Flexion contractures develop at the knees and hips, producing a bent-over posture. Intelligence is normal, although there may be hearing loss. Jansen metaphyseal chondrodysplasia is caused by activating mutations of PTHR1. This G-protein–coupled transmembrane receptor serves as a receptor for both parathyroid hormone and parathyroid hormone-related peptide. Signaling through this receptor serves as a brake on the terminal differentiation of cartilage cells at a critical step in bone growth. Because the mutations activate the receptor, they enhance the braking effect and thereby slow bone growth. Loss-of-function mutations of PTHR1 are observed in Blomstrand chondrodysplasia, whose clinical features are the mirror image of Jansen metaphyseal chondrodysplasia.

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Chapter 697
Disorders Involving Ion Transporters
William A. Horton and Jacqueline T. Hecht

The disorders involving ion transporters result from the functional loss of the sulfate ion transporter called diastrophic dysplasia sulfate transporter (DTDST), which is also referred to as SLC26A2 (solute carrier family 26, member 2). This protein transports sulfate ions into cells and is important for cartilage cells that add sulfate moieties to newly synthesized proteoglycans destined for cartilage extracellular matrix. Matrix proteoglycans are responsible for many of the properties of cartilage that allow it to serve as a template for skeletal development. The clinical manifestations result from defective sulfation of cartilage proteoglycans. In order of decreasing severity, the disorders include: achondrogenesis type 1B, atelosteogenesis type II, diastrophic dysplasia, and a rare recessive form of multiple epiphyseal dysplasia (MIM 226900).

A number of mutant alleles have been found for the DTDST gene; they variably disturb transporter function. The disorders are recessive traits requiring the presence of 2 mutant alleles. The phenotype is determined by the combination of mutant alleles; some alleles are present in more than one disorder.

DIASTROPHIC DYSPLASIA
Diastrophic dysplasia (MIM 22600) is a well-characterized disorder recognized at birth by the presence of very short extremities, clubfoot, and short hands, with proximal displacement of the thumb producing a hitchhiker appearance (Fig. 697-1). The hands are usually deviated in an ulnar direction. Bony fusion of the metacarpophalangeal joints (sympalangism) is common, as is restricted movement of many joints, including hips, knees, and elbows. The external ears often become inflamed soon after birth. The inflammation resolves spontaneously but leaves the ears fibrotic and contracted (cauliflower ear deformity). Many newborns have a cleft palate.

Radiographs reveal short and broad tubular bones with flared metaphyses and flat, irregular epiphyses (Fig. 697-2). The capital femoral epiphyses are hypoplastic, and the femoral heads are broad. The ulnas and fibulas are disproportionately short. Carpal centers may be developmentally advanced; the 1st metacarpal is typically ovoid, and the metatarsals are twisted medially. There may be vertebral abnormalities, including clefts of cervical vertebral lamina and narrowing of the interpedicular distances in the lumbar spine.

Complications are primarily orthopedic and tend to be severe and progressive. The clubfoot deformity in the newborn resists usual treatments, and multiple corrective surgeries are common. Scoliosis typically develops during early childhood. It often requires multiple surgical procedures to control, and it sometimes compromises respiratory function in older children. Despite the orthopedic problems, patients typically have a normal life span and reach adult heights in the 105-130 cm range, depending on the severity of scoliosis. Growth curves are available for diastrophic dysplasia.

Some patients are mildly affected and exhibit slight short stature and joint contractures, no clubfoot or cleft palate, and correspondingly mild radiographic changes. The mild phenotype tends to recur within families. The recurrence risk of this autosomal recessive condition is 25%. Ultrasonographic examination can be employed for prenatal diagnosis, but if DTDST mutations can be identified in the patients or parents, molecular genetic diagnosis is possible.

ACHONDROGENESIS TYPE 1B AND ATELOSTEONEGENESIS TYPE II
Achondrogenesis type 1B (MIM 600972) and atelosteogenesis type II (MIM 256050) are rare recessive lethal chondrodysplasias. The most serious is achondrogenesis type 1B, which demonstrates a severe lack
of skeletal development usually detected in utero or after a miscarriage. The limbs are extremely short, and the head is soft. Skeletal radiographs show poor to missing ossification of skull bones, vertebral bodies, fibulas, and ankle bones. The pelvis is hypoplastic, and the ribs are short. The femurs are short and exhibit a trapezoid shape with irregular metaphyses.

Infants with atelosteogenesis type II are stillborn or die soon after birth; prematurity is common. They exhibit very short limbs, especially the proximal segments. Clubfoot and dislocations of the elbows and knees may be detected. Hypoplasia of vertebral bodies, especially in the cervical and lumbar spine, is found on radiographs. The femora and humeri are hypoplastic and display a club-shaped appearance. The distal limb bones, including the ulna and fibula, are poorly ossified.

Both disorders carry a 25% recurrence risk and are potentially detectable in utero by mutation analysis if the mutant alleles are identified in the parents. Prenatal diagnosis is possible with fetal imaging and/or mutational testing, which is commercially available.

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Bibliography
Chapter 698
Disorders Involving Transcription Factors
William A. Horton and Jacqueline T. Hecht

There are 3 well-delineated disorders involving transcription factors that result in bone dysplasias. **Campomelic dysplasia** is historically considered a chondrodysplasia while **cleidocranial dysplasia** and **nail-patella syndrome**, have been regarded as dysostoses, or abnormalities of single bones. The mutant genes that encode these transcription factors, **SOX9**, **RUNX2 (CBFA1)**, and **LMX1B**, respectively, are members of much larger gene families. **SOX9** is a member of the **SOX** family of genes related to the **SRY** (sex-determining region of the Y chromosome) gene; **RUNX2 (CBFA1)** belongs to the runt family of transcription factor genes, and **LMX1B** is one of the LIM homeodomain gene family. All 3 disorders are a result of haploinsufficiency of the respective gene products; the disorders are dominant traits. For familial cases of cleidocranial dysplasia and nail-patella syndrome, prenatal diagnosis is possible if the mutations are identified. Campomelic dysplasia results from new mutational events and has a low risk of recurrence in subsequent pregnancies.

**CAMPOMELIC DYSPLASIA**
Campomelic dysplasia (MIM 114290) is apparent at birth owing to bowing of long bones (especially in the lower legs), short bones, respiratory distress, and other anomalies that include defects of the cervical spine, central nervous system, heart, and kidneys. In some cases, femoral bowing is minimal (acampomelic campomelic dysplasia). Cases of sex reversal of XY males have been reported; 75% of those with a male karyotype have partial or complete sex reversal. Radiographs confirm the bowing and often show hypoplasia of the scapulae and pelvic bones (Fig. 698-1). Affected infants usually die of respiratory distress in the neonatal period. Complications in children and adolescents who survive include short stature with progressive kyphoscoliosis, hip dislocation, recurrent apnea and respiratory infections, and mild to moderate learning difficulties. Mutational testing is commercially available.

**CLEIDOCRANIAL DYSPLASIA**
Cleidocranial dysplasia (MIM 114290) is recognized in infants because of drooping shoulders, open fontanelles, prominent forehead, mild short stature, and dental abnormalities (Fig. 698-2). Radiographs reveal hypoplastic or absent clavicles, delayed ossification of the cranial bones with multiple ossification centers (wormian bones), and delayed ossification of pelvic bones. The course is usually uncomplicated except for dislocations, especially of the shoulders, and dental anomalies (numerous teeth) that require therapy.

**NAIL-PATELLA SYNDROME**
Dysplasia of the nails, absence or hypoplasia of the patella, abnormalities of the elbow, and spurs or “horns” extending from the iliac bones characterize the nail-patella syndrome (MIM 119600), which is also called osteo-onychodysostosis. Some patients have nephritis that resembles chronic glomerulonephritis. There is a wide spectrum of severity; some patients present in early childhood, whereas others are asymptomatic as adults.

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Disorders Involving Transcription Factors

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Disorders Involving Defective Bone Resorption

William A. Horton and Jacqueline T. Hecht

Osteopetrosis, which has many subtypes, and pyknodysostosis result from defective bone resorption. Overall, bone dysplasias displaying increased bone density are rare.

OSTEOPETROSIS

Two main forms of osteopetrosis have been delineated: a severe autosomal recessive form (MIM 259700) with an incidence of approximately 1 in 250,000 births and a mild autosomal dominant form (MIM 166600) with an incidence of approximately 1 in 20,000 births. Intrinsic disturbances of osteoclast function due to mutations in genes encoding osteoclast-specific subunits of the vacuolar proton pump (TCIRG1, CLCN7) are found in most patients with the recessive form. Mutations of CLCN7 are observed in the dominant form of osteopetrosis. Both types of mutations lead to disturbances of acidification needed for normal osteoclast function. Rarely, patients lack bioactive RANKL (receptor activator of nuclear factor kappa B ligand), the master osteoclastogenic cytokine produced mainly by osteoblasts.

The severe form is usually detected in infancy or earlier because of macrocephaly, hepatosplenomegaly, deafness, blindness, and severe anemia. Radiographs reveal diffuse bone sclerosis and low serum calcium and phosphorus levels with elevated parathyroid hormone levels and normal vitamin D levels. May be detected. Later films show the characteristic bone-within-bone appearance (Fig. 699-1). With time, infants typically fail to thrive and show psychomotor delay and worsening of cranial neuropathies and anemia. Dental problems, osteomyelitis of the mandible, and pathologic fractures are common. Untreated, the most severely affected patients die during infancy; less severely affected patients rarely survive beyond the 2nd decade. Those who survive beyond infancy usually have learning disorders but might have normal intelligence despite hearing and vision loss.

Clinical Manifestations

Most of the manifestations are from failure to remodel growing bones. This leads to narrowing of cranial nerve foramina and encroachment on marrow spaces, which results in secondary complications, such as optic and facial nerve dysfunction, and anemia accompanied by compensatory extramedullary hematopoiesis in the liver and spleen. The unusually dense bones are weak, leading to increased risk of fractures.

The autosomal dominant form of osteopetrosis (Albers-Schönberg disease, osteopetrosis tarda, or marble bone disease) usually manifests during childhood or adolescence with fractures and mild anemia and, less often, as cranial nerve dysfunction, dental abnormalities, or osteomyelitis of the mandible. Skeletal radiographs reveal a generalized...

Figure 699-1 Lateral radiograph showing bone-in-bone appearance that is characteristic of osteopetrosis.
increase in bone density and clubbing of metaphyses. Alternating bands of lucent and dense bands produce a sandwich appearance to vertebral bodies. The radiographic changes are sometimes incidental findings in otherwise asymptomatic adolescents and adults.

**Treatment**

Most of the bone manifestations in severe osteopetrosis caused by intrinsic osteoclast defects can be prevented or reversed by hematopoietic stem cell transplantation, if carried out before development of irreversible secondary complications, such as visual impairment. RANKL replacement therapy may be useful in patients with RANKL deficiency. Calcitriol and interferon-γ have also been used with equivocal results. Symptomatic care, such as dental care, transfusions for anemia, and antibiotic treatment of infections, is important for patients who survive infancy.

**PYKNODYSOOSTOSIS**

An autosomal recessive bone dysplasia, pyknodysoostosis (MIM 265800) manifests in early childhood with short limbs, characteristic facies, an open anterior fontanel, a large skull with frontal and occipital bossing, and dental abnormalities. The hands and feet are short and broad, and the nails may be dysplastic. The sclerae may be blue. Minimal trauma often leads to fractures. Treatment is symptomatic and focused mainly on the management of dental problems and fractures. The prognosis is generally good, and patients typically reach heights of 130-150 cm.

Skeletal radiographs show a generalized increase in bone density. In contrast to many disorders in this group, the metaphyses are normal. Other changes include wide sutures and wormian bones in the skull, a small mandible, and hypoplasia of the distal phalanges (Fig. 699-2).

Several mutations have been found in the gene encoding cathepsin K, a cysteine protease that is highly expressed in osteoclasts. The mutations predict loss of enzyme function, suggesting that there is an inability of osteoclasts to degrade bone matrix and remodel bones.

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Despite great advances in our understanding of the genetic basis of disease in recent years, many chondrodysplasias, or chondrodysplasia clinical phenotypes, remain for which the genetic cause or basic mechanism is poorly understood or not known. Many illustrate features not found in other disorders and have historical significance in the evolution of chondrodysplasia nomenclature and classification.

ELLIS–VAN CREVELD SYNDROME
The Ellis-van Creveld syndrome (MIM 225500), also known as chondroectodermal dysplasia, is a skeletal and an ectodermal dysplasia. The skeletal dysplasia presents at birth with short limbs, especially the middle and distal segments, accompanied by postaxial polydactyly of the hands and sometimes of the feet (Fig. 700-1). Nail dysplasia and dental anomalies (including neonatal, absent, and premature loss of teeth and upper lip defects) constitute the ectodermal dysplasia. Common manifestations also include atrial septal defects and other congenital heart defects.

Skeletal radiographs reveal short tubular bones with clubbed ends, especially the proximal tibia and ulna (Fig. 700-2). Carpal bones display extra ossification centers and fusion; cone-shaped epiphyses are evident in the hands. A bony spur is often noted above the medial aspect of the acetabulum.

Ellis-van Creveld syndrome is an autosomal recessive trait that occurs most often in the Amish. Mutations have been identified in 1 of 2 genes, EVC (EVC1) or EVC2, which map in a head-to-head configuration to chromosome 4p. Mutations of EVC2 are detected in the allelic condition Weyers acrofacial dysostosis. EVC and EVC2 proteins are thought to influence hedgehog signaling in cilia.

Approximately 30% of patients die of cardiac or respiratory problems during infancy. Life span is otherwise normal; adult heights range from 119-161 cm.

ASPHYXIATING THORACIC DYSTROPHY
(see also Chapter 417.3)
Asphyxiating thoracic dystrophy (MIM 208500), or Jeune syndrome, is an autosomal recessive chondrodysplasia that resembles Ellis-van Creveld syndrome. Newborn infants present with a long, narrow thorax and respiratory insufficiency associated with pulmonary hypoplasia. Neonates often die. Other neonatal manifestations include slightly short limbs and postaxial polydactyly. This condition results from a disturbance of primary cilia, most often from mutations of the gene encoding cytoplasmic dynein 2 heavy chain 1 (DYN2HC1).

Skeletal radiographs show very short ribs with anterior expansion. Tubular limb bones are short with bulbous ends; cone-shaped epiphyses occur in hand bones. The iliac bones are short and square with a spur above the medial aspect of the acetabulum.

If infants survive the neonatal period, respiratory function usually improves as the rib cage grows. Surgery that produces lateral thoracic expansion improves rib growth and enhances chest wall dimensions. Progressive renal dysfunction often develops during childhood. Intestinal malabsorption and hepatic dysfunction have also been reported.
for Which Defects Are Poorly Understood or Unknown

**CARTILAGE-HAIR HYPOPLASIA**
Cartilage-hair hypoplasia (CHH; MIM 250250) is also known as metaphyseal chondrodysplasia–McKusick type. It is recognized during the 2nd yr because of growth deficiency affecting the limbs, accompanied by flaring of the lower rib cage, a prominent sternum, and bowing of the legs. The hands and feet are short, and the fingers are very short with extreme ligamentous laxity. The hair is thin, sparse, and light colored, and nails are hypoplastic. The skin is hypopigmented.

Radiographs show short tubular bones with flared, irregularly mineralized, and cupped metaphyses (Fig. 700-3). The knees are more affected than are the hips, and the fibula is disproportionately longer.
than the tibia. The metacarpals and phalanges are short and broad. Spinal radiographs reveal mild platyspondyly.

Nonskeletal manifestations associated with CHH include immunodeficiency (T-cell abnormalities, neutropenia, leukopenia, and susceptibility to chickenpox; children also may have complications from smallpox and polio vaccinations), malabsorption, celiac disease, and Hirschsprung disease. Adults are at risk for malignancy, especially non-Hodgkin lymphoma and skin tumors. Adults reach heights of 107-157 cm.

CHH shows autosomal recessive inheritance. Its highest prevalence is in the Amish and Finnish populations. It results from mutations of a gene coding for a large untranslated RNA component of an enzyme complex involved in processing mitochondrial RNA. Loss of this gene product interferes with processing of both messenger RNA and ribosomal RNA. Loss of ribosomal RNA processing correlates with the extent of bone dysplasia, whereas loss of messenger RNA processing correlates with degree of hair hypoplasia, immunodeficiency, and hematologic abnormality. Mutations of the RNA component of mitochondrial RNA processing are occasionally detected in patients with mild metaphyseal dysplasia lacking the extraskeletal features characteristic of CHH. Prenatal diagnosis is available if the mutation is identified either in the patient or parents.

METATROPIC DYSPLASIA

Metatropic dysplasia (MIM 156530) is an autosomal dominant disorder resulting from heterozygous mutations of \textit{TRPV4} (transient receptor potential vanilloid family 4), which encodes a calcium-permeable cation channel. Newborn infants present with a long narrow trunk and short extremities. A tail-like appendage sometimes extends from the base of the spine. Odontoid hypoplasia is common and may be associated with cervical instability. Kyphoscoliosis appears in late infancy and progresses through childhood, often becoming severe enough to compromise cardiopulmonary function. The joints are large and become progressively restricted in mobility, except in the hands. Contractures often develop in the hips and knees during childhood. Although severely affected infants can die at a young age from respiratory failure, patients usually survive, although they can become disabled as adults from the progressive musculoskeletal deformities. Adult heights range from 110-120 cm.

Skeletal radiographs show characteristic changes dominated by severe platyspondyly and short tubular bones with expanded and deformed metaphyses that exhibit a dumbbell appearance (Fig. 700-4). The pelvic bones are hypoplastic and exhibit a halberd appearance because of a small sacrosciatic notch and a notch above the lateral margin of the acetabulum.

SPONDYLOMETAPHYSEAL DYSPLASIA, KOZLOWSKI TYPE

The Kozlowski type of spondylometaphyseal dysplasia (MIM 184252) is an autosomal dominant allelic disorder to metatropic dysplasia caused by \textit{TRPV4} mutations. Mutations of \textit{TRPV4} have also been identified in autosomal dominant brachyolmia, whose phenotype is dominated by progressive scoliosis and platyspondyly on x-rays.

The Kozlowski type of spondylometaphyseal dysplasia manifests in early childhood with mild short stature involving mostly the trunk and a waddling gait. The hands and feet may be short and stubby. Radiographs show flattening of vertebral bodies. The metaphyses of tubular bones are widened and irregularly mineralized, especially at the proximal femur. The pelvic bones manifest mild hypoplasia. Scoliosis can develop during adolescence. The disorder is otherwise uncomplicated, and manifestations are limited to the skeleton. Adults reach heights of 130-150 cm.

DISORDERS INVOLVING FILAMINS

Mutations of genes encoding filamin A and filamin B proteins have been detected in diverse disorders of skeletal development: filamin A mutations in otopalatodigital syndromes type 1 and 2, frontometaphyseal dysplasia and Melnick-Needles syndrome (MIM 311300, 304120, 305620, 309350) and filamin B mutations in Larsen syndrome and perinatal lethal atelosteogenesis types I and III and Boomerang dysplasia (MIM 150250, 108720, 108721, 112310). Filamins functionally connect extracellular to intracellular structural proteins, thereby linking cells to their local microenvironment, which is essential for skeletal development and growth.
Table 700-1  Juvenile Osteochondroses

<table>
<thead>
<tr>
<th>EPONYM</th>
<th>AFFECTED REGION</th>
<th>AGE AT PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legg-Calvé-Perthes disease</td>
<td>Capital femoral epiphysis</td>
<td>3-12 yr</td>
</tr>
<tr>
<td>Osgood-Schlatter disease</td>
<td>Tibial tubercle</td>
<td>10-16 yr</td>
</tr>
<tr>
<td>Sever disease</td>
<td>Os calcaneus</td>
<td>6-10 yr</td>
</tr>
<tr>
<td>Freiberg disease</td>
<td>Head of second metatarsal</td>
<td>10-14 yr</td>
</tr>
<tr>
<td>Scheuermann disease</td>
<td>Vertebral bodies</td>
<td>Adolescence</td>
</tr>
<tr>
<td>Blount disease</td>
<td>Medial aspect of proximal tibial epiphysis</td>
<td>Infancy or adolescence</td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>Subchondral regions of knee, hip, elbow, and ankle</td>
<td>Adolescence</td>
</tr>
</tbody>
</table>

**JUVENILE OSTEOCHONDROSSES**

The juvenile osteochondroses are a heterogeneous group of disorders in which regional disturbances in bone growth cause noninflammatory arthropathies. Table 700-1 summarizes the juvenile osteochondroses. Some have localized pain and tenderness (Freiberg disease, Osgood-Schlatter disease [see Chapter 677.4], osteochondritis dissecans [see Chapter 677.3]), whereas others present with painless limitation of joint movement (Legg-Calvé-Perthes disease [see Chapter 678.3], Scheuermann disease [see Chapter 679.4]). Bone growth may be disrupted, leading to deformities. The diagnosis is usually confirmed radiographically, and treatment is symptomatic. The pathogenesis of these disorders is believed to involve ischemic necrosis of primary and secondary ossification centers. Although familial forms have been reported, these disorders usually occur sporadically.

**CAFFEY DISEASE (INFANTILE CORTICAL HYPEROSTOSIS)**

This is a rare disorder of unknown etiology characterized by cortical hyperostosis with inflammation of the contiguous fascia and muscle. It is often sporadic, but both autosomal dominant and autosomal recessive inheritance have been reported. In 3 unrelated families with autosomal dominant inheritance, a linkage to mutations of the COL1A1 gene (codes for the α1 chain of type I collagen) has been reported.

Prenatal and more often postnatal onset have been described. Prenatal onset may be mild (autosomal dominant) or severe (autosomal recessive). Severe prenatal disease is characterized by typical bone lesions, polyhydramnios, hydrops fetalis, severe respiratory distress, prematurity, and high mortality. Onset in infancy (younger than 6 mo; average: 10 wk) is most common; manifestations include the sudden onset of irritability, swelling of contiguous soft tissue that precedes the cortical thickening of the underlying bones, fever, and anorexia. The swelling is painful with a wood-like induration but with minimal warmth or redness; suppuration is absent. There are unpredictable remissions and relapses; an episode can last 2 wk to 3 mo. The most common bones involved include the mandible (75%) (Fig. 700-5), the clavicle, and the ulna. If swelling is not prominent or visible, the diagnosis might not be evident.

Laboratory features include elevated erythrocyte sedimentation rate and serum alkaline phosphatase as well as, in some patients, increased serum prostaglandin E levels. There may be thrombocytosis and anemia. The radiographic features include soft-tissue swelling and calcification and cortical hyperostosis (Fig. 700-6). All bones may be affected except the phalanges or vertebral bodies. The differential diagnosis includes other causes of hyperostosis such as chronic vitamin A intoxication, prolonged prostaglandin E infusion in children with dactylitis dependent congenital heart disease, primary bone tumors, and scurvy.

Complications are unusual but include pseudoparalysis with limb or scapula involvement, pleural effusions (rib), torticollis (clavicle), mandibular asymmetry, bone fusion (ribs or ulna and radius), and bone angulation deformities (common with severe prenatal onset).

Treatment includes indomethacin and prednisone (if there is a poor response to indomethacin).

**FIBRODYSPLASIA OSSIFICANS PROGRESSIVE**

Fibrodysplasia ossificans progressive (FOP) (MIM 135100) is a rare and severely disabling disorder characterized by progressive extraskel-etal bone formation in soft connective tissues including muscles, tendons, ligaments, fascia, and aponeuroses. With exception of deform-ity of the large toes, infants are normal at birth. Episodes of painful soft-tissue swelling with inflammation usually begin in early childhood initially involving the upper back and neck and later the entire trunk and extremities. Repeated episodes (flare-ups) slowly transform the soft tissues into bands or plates of bone that span joints and progress-ively limit movement and mobility. Episodes are often triggered by injury, intramuscular injections and viral infection. Most patients are wheelchair bound by their late teens. The average life span is approxi-mately 40 yr, with death usually resulting from complications of tho-racic insufficiency.

Figure 700-5  Facies in infantile cortical hyperostosis. In almost all cases, the changes have appeared before the 5th mo of life. Unilateral swelling of the left cheek and left side of the jaw in an infant 12 wk of age. (From Slovis TL: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby.)
FOP results from heterozygous activating mutations of the gene encoding the bone morphogenetic protein (BMP) type I receptor, activin A receptor type I (ACVR1). Patients with classic FOP have the same missense ACVR1 mutation, which enhances BMP signaling, which, in turn, induces inflammation and aberrant endochondral ossification through mechanisms that are poorly understood. Environmental factors such as injury play an important role in triggering these events. ACVR1 mutations usually occur sporadically, but autosomal dominant transmission has rarely been observed.

There is no definitive treatment for FOP. Supportive care includes avoidance of injury-prone physical activities, intramuscular injections including immunizations and overstretching of the jaw during dental procedures. Corticosteroids and other antiinflammatory agents reduce inflammation during flare-ups. Studies in FOP animal models suggest that BMP type I kinase inhibitors and retinoic acid receptor γ agonists, which block chondrogenesis, the initial step in endochondral ossification, may be useful therapies in the future.

Bibliography is available at Expert Consult.
Bibliography


Osteoporosis is fragility of the skeletal system and a susceptibility to fractures of the long bones or vertebral compressions from mild or inconsequential trauma. Osteogenesis imperfecta (OI) (brittle bone disease), the most common genetic cause of osteoporosis, is a generalized disorder of connective tissue. The spectrum of OI is extremely broad, ranging from forms that are lethal in the perinatal period to a mild form in which the diagnosis may be equivocal in an adult.

**ETIOLOGY**
Structural or quantitative defects in type I collagen cause the full clinical spectrum of OI (types I-IV). Type I collagen is the primary component of the extracellular matrix of bone and skin. Between 10 and 15% of patients clinically indistinguishable from OI do not have a molecular defect in type I collagen (Table 701-1). These cases are caused by defects in genes whose protein products interact with type I collagen. One group of patients has overmodified collagen, with similar biochemical findings to those with collagen structural defects and severe or lethal OI bone dysplasia. These cases are caused by recessive null mutations in any of the 3 components of the collagen prolyl 3-hydroxylation complex, prolyl 3-hydroxylase 1 (coded by the LEPRE1 gene on chromosome 1p34.1) or its associated protein, CRTAP, or cyclophilin B (CyPB, encoded by PPIB). A second set of cases without collagen defects have biochemically normal collagen. Defects in IFITM5 and SERPINF1 account for defects in mineralization in types V and VI OI, while mutations in SERPINH1, encoding the collagen chaperone HSP47, and FKBP10, encoding the peptidyl-prolyl cis-trans isomerase FKBP65, cause types X and XI OI, respectively. Rare mutations in BMP1, TMEM38B and WNT1 also cause recessive OI; the genetic defect in some individuals is still unknown.

**EPIDEMIOLOGY**
The autosomal dominant forms of OI occur equally in all racial and ethnic groups, whereas recessive forms occur predominantly in ethnic groups with consanguineous marriages. The West African founder mutation for type VIII OI has a carrier frequency of 1 in 200-300 among African-Americans. The incidence of OI detectable in infancy is approximately 1 in 20,000. There is a similar incidence of the mild form OI type I.

**PATHOLOGY**
The collagen structural mutations cause OI bone to be globally abnormal. The bone matrix contains abnormal type I collagen fibrils and relatively increased levels of types III and V collagen. Several noncollagenous proteins of bone matrix are also reduced. Bone cells contribute to OI pathology, with abnormal osteoblast differentiation and increased numbers of active bone resorbing osteoclasts. The hydroxyapatite crystals deposited on this matrix are poorly aligned with the long axis of fibrils, and there is paradoxical hypermineralization of bone.

**PATHOGENESIS**
Type I collagen is a heterotrimer composed of 2 α1(I) chains and 1 α2(I) chain. The chains are synthesized as procollagen molecules with short globular extensions on both ends of the central helical domain. The helical domain is composed of uninterrupted repeats of the sequence Gly-X-Y, where Gly is glycine, X is often proline, and Y is often hydroxyproline. The presence of glycine at every third residue is crucial to helix formation because its small side chain can be accommodated in the interior of the helix. The chains are assembled into trimers at their carboxyl ends; helix formation then proceeds linearly in a carboxyl to amino direction. Concomitant with helix assembly and formation, helical proline and lysine residues are hydroxylated by prolyl 4-hydroxylase and lysyl hydroxylase and some hydroxylysine residues are glycosylated.

Collagen structural defects are predominantly of 2 types: 80% are point mutations causing substitutions of helical glycine residues or crucial residues in the C-propeptide by other amino acids, and 20% are single exon splicing defects. The clinically mild OI type I has a quantitative defect, with null mutations in 1 α1(I) allele leading to a reduced amount of normal collagen.

The glycine substitutions in the 2 α chains have distinct genotype-phenotype relationships. One-third of mutations in the α1 chain are lethal, and those in α2(I) are predominantly nonlethal. Two lethal regions in α1(I) align with major ligand binding regions of the collagen helix. Lethal mutations in α2(I) occur in 8 regularly spaced clusters along the chain that align with binding regions for matrix proteoglycans in the collagen fibril.
**Table 701-1: Osteogenesis Type, Gene Defects, and Phenotypes**

<table>
<thead>
<tr>
<th>OSTEOGENESIS IMPERFECTA TYPE</th>
<th>GENE DEFECT</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOMINANT INHERITANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical Silence Types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>COL1A1 null allele</td>
<td>Mild, nondeforming</td>
</tr>
<tr>
<td>II</td>
<td>COL1A1 or COL1A2</td>
<td>Lethal perinatal</td>
</tr>
<tr>
<td>III</td>
<td>COL1A1 or COL1A2</td>
<td>Progressively deforming</td>
</tr>
<tr>
<td>IV</td>
<td>COL1A1 or COL1A2</td>
<td>Moderately deforming</td>
</tr>
<tr>
<td><strong>COL1-Mutation Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>IFITM5</td>
<td>Distinct histology</td>
</tr>
<tr>
<td><strong>RECESSIVE INHERITANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineralization Defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI/3-Hydroxylation Defect</td>
<td>SERPINF1</td>
<td>Distinct histology</td>
</tr>
<tr>
<td>VII</td>
<td>CRTAP</td>
<td>Severe to lethal</td>
</tr>
<tr>
<td>VIII</td>
<td>LEPRE1</td>
<td>Severe to lethal</td>
</tr>
<tr>
<td>IX</td>
<td>PP1B</td>
<td>Moderate to lethal</td>
</tr>
<tr>
<td>Chaperone Defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>SERPINH1</td>
<td>Severe</td>
</tr>
<tr>
<td>XI</td>
<td>FKBPI0</td>
<td>Progressive deforming, Bruck syndrome 1</td>
</tr>
<tr>
<td>XII</td>
<td>BMP1</td>
<td>Severe, high bone mass case</td>
</tr>
<tr>
<td><strong>UNCLASSIFIED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc-finger transcription factor defect</td>
<td>SP7</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cation channel defect</td>
<td>TMEM38B</td>
<td>Moderate</td>
</tr>
<tr>
<td>WNT signaling pathway defect</td>
<td>WNT1</td>
<td>Moderate, progressively deforming</td>
</tr>
</tbody>
</table>


Classical OI (Sillence types I-IV) is an autosomal dominant disorder, as is type V OI. Some familial recurrences of OI are caused by parental mosaicism for dominant collagen mutations. Recessive OI accounts for 5-7% of new OI in North America. Three recessive types are caused by null mutations in the genes coding for the components of the collagen prolyl 3-hydroxylation complex in the endoplasmic reticulum (LEPRE1, CRTAP, or PP1B). It is not yet clear whether absence of the complex itself or of the modification is the crucial feature of these types of recessive OI. Other recessive types are caused by null mutations in genes whose products are involved in collagen folding (SERPINH1, FKBPI0), or mineralization (SERPINF1).

**CLINICAL MANIFESTATIONS**

Classical OI was described with the triad of fragile bones, blue sclerae, and early deafness, although most cases do not have all of these features. The Sillence classification divides OI into 4 types based on clinical and radiographic criteria. Types V and VI were later proposed based on histologic distinctions. Subsequent types VII-XII were based on identification of the molecular defect, followed by clinical description.

**Osteogenesis Imperfecta Type I (Mild)**

OI type I is sufficiently mild that it is often found in large pedigrees. Many type I families have blue sclerae, recurrent fractures in childhood, and presenile hearing loss (30-60%). Both types I and IV are divided into A and B subtypes, depending on the absence (A) or presence (B) of dentinogenesis imperfecta. Other possible connective tissue abnormalities include hyperextensible joints, easy bruising, thin skin, joint laxity, scoliosis, wormian bones, hernia, and mild short stature compared with family members. Fractures result from mild to moderate trauma but decrease after puberty.

**Osteogenesis Imperfecta Type II (Perinatal Lethal)**

Infants with OI type II may be stillborn or die in the 1st yr of life. Birthweight and length are small for gestational age. There is extreme fragility of the skeleton and other connective tissues. There are multi-intrauterine fractures of long bones, which have a crumpled appearance on radiographs. There are striking micromelia and bowing of extremities; the legs are held abducted at right angles to the body in the frogleg position. Multiple rib fractures create a beaded appearance, and the small thorax contributes to respiratory insufficiency. The skull is large for body size, with enlarged anterior and posterior fontanels. Sclerae are dark blue-gray. The cerebral cortex has multiple neuronal migration and other defects (agyria, gliosis, periventricular leukomalacia).

**Osteogenesis Imperfecta Type III (Progressive Deforming)**

OI type III is the most severe nonlethal form of OI and results in significant physical disability. Birthweight and length are often low normal. Fractures usually occur in utero. There is relative macrocephaly and triangular facies (Fig. 701-1). Postnatally, fractures occur from inconsequential trauma and heal with deformity. Disorganization of the bone matrix results in a “popcorn” appearance at the metaphyses (Fig. 701-2). The rib cage has flaring at the base, and pectal deformity is frequent. Virtually all type III patients have scoliosis and vertebral compression. Growth falls below the curve by the 1st yr; all type III patients have extreme short stature. Scleral hue ranges from white to blue. Dentinogenesis imperfecta, hearing loss, and kyphoscoliosis may be present or develop over time.

**Osteogenesis Imperfecta Type IV (Moderately Severe)**

Patients with OI type IV can present at birth with in utero fractures or bowing of lower long bones. They can also present with recurrent fractures after ambulation and have normal to moderate short stature. Most children have moderate bowing even with infrequent fractures. Children with OI type IV require orthopedic and rehabilitation intervention, but they are usually able to attain community ambulation skills. Fracture rates decrease after puberty. Radiographically, they are osteoporotic and have metaphyseal flaring and vertebral compressions. Patients with type IV have moderate short stature. Scleral hue may be blue or white.
Bone 701-1

Infant with type III osteogenesis imperfecta displays shortened bowed extremities, thoracic deformity, and relative macrocephaly.

Osteogenesis Imperfecta Type V (Hyperplastic Callus) and Type VI Hyperosteooidosis (Mineralization Defect)

Types V and VI OI patients clinically have OI similar in skeletal severity to type IV, but they have distinct findings on bone histology. Type V patients also usually have some combination of hyperplastic callus, calcification of the interosseous membrane of the forearm, and/or a radiodense metaphyseal band. They constitute <3% of OI populations. All type V OI patients are heterozygous for the same mutation in IFITM5, which generates a novel start codon for the bone protein Bril. Ligamentous laxity may be present; blue sclera or dentinogenesis imperfecta are not present. Patients with type VI OI have progressive deforming OI that does not manifest at birth. They have distinctive bone histology with broad osteoid seams and fish-scale lamellation under polarized light.

Osteogenesis Imperfecta Types VII, VIII, and IX (Autosomal Recessive)

Types VII and VIII patients overlap clinically with types II and III OI but have distinct features including white sclerae, rhizomelia, and small to normal head circumference. Surviving children have severe osteochondrodysplasia with extreme short stature and dual-energy x-ray absorptiometry L1-L2 z-scores in the −6 to −7 range. Type IX OI is very rare (only 8 cases reported). The severity is quite broad, ranging from lethal to moderately severe. These children have white sclerae but do not have rhizomelia.

Osteogenesis Imperfecta Types X and XI (Autosomal Recessive)

Only 1 patient with type X OI has been reported; the child had severe OI with white sclerae and died of respiratory causes at age 3 yr. Type XI OI is a more prevalent recessive form with a moderate to severe skeletal phenotype, including white sclerae and normal teeth. Congenital contractures of large joints may occur with the same mutations that cause only skeletal fragility, even in sibships. At the opposite end of the spectrum, a deletion of a single tyrosine residue causes Kusakokwim syndrome, a congenital contracture disorder with very mild vertebral findings and osteopenia.

High Bone Mass Osteogenesis Imperfecta (Cleavage of the Procollagen C-Propeptide)

Autosomal dominant mutations in the C-propeptide cleavage site of procollagen or in the enzyme responsible for its cleavage cause bone fragility with normal or elevated dual-energy x-ray absorptiometry bone density z-scores. Individuals with dominant mutations have normal stature, white sclerae and teeth and mild to moderate OI. Null mutations in BMP1 lead to a more severe skeletal phenotype with short stature, scoliosis and bone deformity, because BMP1 has other substrates in addition to type I collagen.

Other Genes for Osteogenesis Imperfecta

A very small percentage of OI patients have bone dysplasia that cannot be accounted for by mutations in the genes described above.

LABORATORY FINDINGS

DNA sequencing is the first diagnostic laboratory test; several diagnostic labs offer panels to test for dominant and recessive OI. Mutation identification is useful to determine the type with certainty and to facilitate family screening and prenatal diagnosis. It is also possible to screen for type VI OI by determination of serum pigment epithelium-derived factor level, which is severely reduced in this type.

If dermal fibroblasts are obtained these can be useful for determining the level of transcripts of the candidate gene and also for collagen biochemical testing, which is positive in most cases of types I-IV and IX OI and all cases of VII/VIII OI. In OI type I, the reduced amount of type I collagen results in an increase in the ratio of type III to type I collagen on gel electrophoresis.

Severe OI can be detected prenatally by level II ultrasonography as early as 16 wk of gestation. OI and thanatophoric dysplasia may be confused. Fetal ultrasonography might not detect OI type IV and rarely detects OI type I. For recurrent cases, chorionic villus biopsy can be used for biochemical or molecular studies. Amniocytes produce false-positive biochemical studies but can be used for molecular studies in appropriate cases.

In the neonatal period, the normal to elevated alkaline phosphatase levels present in OI distinguish it from hypophosphatasia.

COMPLICATIONS

The morbidity and mortality of OI are cardiopulmonary. Recurrent pneumonias and declining pulmonary function occur in childhood, and cor pulmonale is seen in adults.

Neurologic complications include basilar invagination, brainstem compression, hydrocephalus, and syringohydromyelia. Most children with OI types III and IV have basilar invagination, but brainstem compression is uncommon. Basilar invagination is best detected with spiral CT of the craniocervical junction (Fig. 701-3).

TREATMENT

There is no cure for OI. For severe nonlethal OI, active physical rehabilitation in the early years allows children to attain a higher functional level than orthopedic management alone. Children with OI type I and some with type IV are spontaneous ambulators. Children with types III, IV, V, VI, and XI OI benefit from gait aids and a program of swimming and conditioning. Severely affected patients require a wheelchair for community mobility but can acquire transfer and self-care skills. Teens with OI can require psychologic support with body image issues. Growth hormone improves bone histology in growth-responsive children (usually types I and IV).

Orthopedic management of OI is aimed at fracture management and correction of deformity to enable function. Fractures should be promptly splinted or cast; OI fractures heal well, and cast removal should be aimed at minimizing immobilization osteoporosis. Correction of long bone deformity requires an osteotomy procedure and placement of an intramedullary rod.
A several-year course of treatment of children with OI with bisphosphonates (IV pamidronate or oral olpadronate or risedronate) confers some benefits. Bisphosphonates decrease bone resorption by osteoclasts; OI patients have increased bone volume that still contains the defective collagen. Bisphosphonates are more beneficial for vertebrae (trabecular bone) than long bones (cortical bone). Treatment for 1-2 yr results in increased L1-4 dual-energy x-ray absorptiometry and, more importantly, improved vertebral compressions and area, which can prevent or delay the scoliosis of OI. Relative risk of long bone fractures is modestly decreased. However, the material properties of long bones are weakened by prolonged treatment and non-union after osteotomy is increased. There is no effect of bisphosphonates on mobility scores, muscle strength, or bone pain. Limiting treatment duration to 2-3 yr in mid-childhood can maximize benefits and minimize detriment to cortical material properties. Benefits appear to persist several years after the treatment interval. Side effects include abnormal long bone remodeling, increased incidence of fracture non-union, and osteopetrotic-like brittleness to bone.

**PROGNOSIS**

OI is a chronic condition that limits both life span and functional level. Infants with OI type II usually die within months to a year of life. An occasional child with radiographic type II and extreme growth deficiency survives to the teen years. Persons with OI type III have a reduced life span with clusters of mortality from pulmonary causes in early childhood, the teen years, and the 40s. OI types I, IV, and V OI
are compatible with a full life span. The oldest reported individuals with type VIII are in their 3rd decade, and some with type XI are in their 4th decade. The long-term prognosis for most recessive types is still emerging, and many adults with OI have not had molecular testing.

Individuals with OI type III are usually wheelchair dependent. With aggressive rehabilitation, they can attain transfer skills and household ambulation. OI type IV children usually attain community ambulation skills either independently or with gait aids.

GENETIC COUNSELING

For autosomal dominant OI, the risk of an affected individual passing the gene to the individual's offspring is 50%. An affected child usually has about the same severity of OI as the parent; however, there is variability of expression, and the child's condition can be either more or less severe than that of the parent. The empirical recurrence risk to an apparently unaffected couple of having a second child with OI is 5-7%; this is the statistical chance that 1 parent has germline mosaicism. The collagen mutation in the mosaic parent is present in some germ cells and may be present in somatic tissues. If a parent is a mosaic carrier, the risk of recurrence may be as high as 50%.

For recessive OI, the recurrence risk is 25% per pregnancy. No known individual with severe nonlethal recessive OI has had a child.

Bibliography is available at Expert Consult.
Chapter 701  Osteogenesis Imperfecta  3384.e1

Bibliography
Marfan syndrome (MFS) is an inherited, systemic, connective tissue disorder caused by mutations in the gene encoding the extracellular matrix (ECM) protein fibrillin-1. It is primarily associated with skeletal, cardiovascular, and ocular pathology. The diagnosis is based on clinical findings, some of which are age dependent.

**EPIDEMIOLOGY**

The incidence is reported to be 1 in 10,000 live births and approximately one-fourth of cases are sporadic. The disorder shows autosomal dominant inheritance, with high penetrance, but variable expression; both interfamilial and intrafamilial clinical variation is common. There is no racial or gender preference.

**PATHOGENESIS**

MFS is associated with abnormal production, matrix deposition and/or stability of fibrillin-1, a 350-kDa ECM protein that is the major constituent of microfibrils, with prominent disruption of microfibrils and elastic fibers in diseased tissues. The fibrillin-1 (FBN1) locus resides on the long arm of chromosome 15 (15q21), and the gene is composed of 65 exons. Linkage analysis suggests an absence of locus heterogeneity and the involvement of FBN1 has been demonstrated in >90% of cases, with more than 1,000 disease-causing mutations identified to date (the majority of which are missense point mutations and unique to a given family). With the exception of an early onset and severe presentations of the disease associated with some mutations in exons 26-27 and 31-32, no clear genotype–phenotype correlation has been demonstrated in most MFS cases. With the exception of an early onset and severe presentations of the disease associated with some mutations in exons 26-27 and 31-32, no clear genotype–phenotype correlation has been demonstrated to date.

Additional research identified a cytokine-regulatory role for fibrillin-1 manifesting this structural insufficiency with accelerated degeneration. Aberrant TGF-β signaling might also play a role in the wider spectrum of manifestations of MFS. Increased TGF-β signaling has been observed in other tissues in MFS mice, including the developing lung, mitral valve, and skeletal muscle. Treatment of these mice with agents that antagonize TGF-β attenuates or prevents pulmonary emphysema, myxomatous degeneration of the mitral valve, and skeletal muscle myopathy. The prominent role of TGF-β dysregulation in the pathogenesis of MFS was further validated by the discovery and characterization of another aortic aneurysm syndrome, Loeys-Dietz syndrome, in which patients have mutations in the TGF-β receptors and share many overlapping clinical features with MFS (see “Differential Diagnosis” below).

**CLINICAL MANIFESTATIONS**

MFS is a multisystem disorder, with cardinal manifestations in the skeletal, cardiovascular, and ocular systems.

**Skeletal System**

Overgrowth of the long bones (dolichostenomelia) is often the most obvious manifestation of MFS and may produce a reduced upper segment: lower segment ratio (US:LS) or an arm span to height ratio >1.05 times. Abnormal ratios are US:LS <1 for ages 0-5 yr, US:LS <0.95 for ages 6-7 yr, US:LS <0.9 for ages 8-9 yr, and <0.85 above age 10 yr. Anterior chest deformity is likely the result of excessive rib growth, pushing the sternum either outward (pectus carinatum) or inward (pectus excavatum). Abnormal curvatures of the spine (most commonly thoracolumbar scoliosis) may also partly result from increased vertebral growth. Other skeletal features include an inward bulging of the acetabulum into the pelvic cavity (protrusio acetabuli), flatfeet (pes planus), and joint hypermobility or joint contractures. Long and slender fingers in relation to the palm of the hand (arachnodactyly) is generally a subjective finding. The combination of arachnodactyly and hypermobile joints is examined by the Walker-Murdoch or wrist sign, which is positive if there is full overlap of the distal phalanges of the thumb and fifth finger when wrapped around the contralateral wrist (Fig. 702-1), and the Steinberg or thumb sign, which is present when the distal phalanx of the thumb fully extends beyond the ulnar border of the hand when folded across the palm (Fig. 702-1). Contracture of the fingers (camptodactyly) and elbows is commonly observed. A selection of craniofacial manifestations may be present including a long narrow skull (dolichocephaly), deep-set eyes (enophthalmos), recessed lower mandible (retrognathia) or small chin (micrognathia), flattening of the midface (malar hypoplasia), a high-arching palate, and downward-slanting palpebral fissures (Fig. 702-2).

**Cardiovascular System**

Within the heart, thickening of the atrioventricular valves is common and often associated with valvular prolapse. Variable degrees of regurgitation may be present. In children with early onset and severe MFS,
insufficiency of the mitral valve can lead to congestive heart failure, pulmonary hypertension and death in infancy; this manifestation is the leading cause of morbidity and mortality in young children with the disorder. Supraventricular arrhythmias and ventricular dysrhythmias may be seen in association with mitral valve dysfunction, and there is an increased prevalence of prolonged QT interval. Dilated cardiomyopathy occurs with increased prevalence in patients with MFS, most often attributed to volume overload imposed by valve regurgitation. Aortic valve dysfunction is generally a late occurrence and attributed to stretching of the aortic annulus by an expanding aortic root aneurysm.

Aortic aneurysm, dissection and rupture, principally at the level of the sinuses of Valsalva (aortic root), remains the most life-threatening manifestations of MFS, prompting lifelong monitoring by echocardiography or other imaging modalities. In severe cases, the aneurysm may be present in utero, but in mild examples, it may be absent or never exceed dimensions that require clinical intervention. Aortic dimensions must be interpreted in comparison to age-dependent nomograms. The most important risk factor for aortic dissection are the maximal aortic root size and a positive family history. The characteristic histologic findings from aortae of patients with MFS include cystic medial necrosis of the tunica media and disruption of elastic lamellae. Cystic medial necrosis describes the focal apoptosis and disappearance of vascular smooth muscle cells and elastic fibers from the of the tunica media of the aortic wall, and subsequent deposition of mucin-like material in the cystic space. These changes produce a thicker, less distensible and stiffer aorta, which is more prone to aortic dissection. Most patients experiencing acute aortic dissection present with classic symptoms including sudden-onset, severe, tearing chest pain, often radiate into the back. The dissection typically starts at the aortic root and may remain confined to the ascending aorta (type II) or continue into the descending aorta (type I). Acute-onset congestive heart failure may occur if aortic valve function is compromised and patients may suffer cerebrovascular injury depending on the involvement of the carotid arteries. Involvement of the coronary arteries may herald sudden cardiac death, secondary to myocardial infarction or rupture into the pericardial sac with subsequent pericardial tamponade. Chronic aortic dissection usually occurs more insidiously, often without chest pain. Dilation of the main pulmonary artery is common but does not typically cause any clinical sequelae. Enlargement of the

**Figure 702-1** Note the joint laxity (A), Steinberg thumb sign (B), ability to join thumb and fifth finger around the wrist (Walker-Murdoch sign) (C), pes planus (D), and striae over hips and back (E). (From Jones KL, Jones MC, del Campo M: Smith’s recognizable patterns of human malformation, ed 7, Philadelphia, 2013, WB Saunders, Fig. 2, p. 616; A-D courtesy Dr. Lynne M. Bird, Rady Children’s Hospital, San Diego, CA.)
descending thoracic or abdominal aorta can also occur, although relatively rarely.

**Ocular System**
Dislocation of the ocular lens (ectopia lentis) occurs in approximately 60-70% of patients, although it is not unique to the disorder. Other ocular manifestations include early and severe myopia, flat cornea, increased axial length of the globe, hypoplastic iris, and ciliary muscle hypoplasia, causing decreased miosis. Patients are also predisposed to retinal detachment and early cataracts or glaucoma.

**Other Systems**
There is an increased incidence of pulmonary disease in MFS; progressive anterior chest deformity or thoracic scoliosis may contribute to a restrictive pattern of lung disease. A widening of the distal airspaces predisposes patients to spontaneous pneumothorax, which occurs in up to 15% of patients. Assessment of pulmonary volumes and function should account for long bone overgrowth affecting the lower extremities, which can lead to a reduction in the normalized forced vital capacity and total lung capacity. If normalized to thoracic size or sitting height, pulmonary function testing is often normal in patients with the disorder.

MFS patients typically have normal skin texture and elasticity. The most common skin finding is stretch marks—pinkish, scar-like lesions that later become white (striae atrophicae), which occur in about one-third of patients (see Fig. 702-1). These may occur in the absence of obesity, rapid gain in muscle mass, or pregnancy, and at sites not associated with increased skin distention (i.e., the anterior shoulder or lower back). Another common manifestation is congenital or acquired inguinal hernia. There is also an increased risk of surgical and recurrent hernias in the Marfan population.

Widening of the dural sac or root sleeves (dural ectasia) is present in 63-92% of MFS patients. Although dural ectasia can result in lumbar back pain, it is often asymptomatic and should be assessed by lumbo-sacral imaging with CT or MRI.

**DIAGNOSIS**
Given the complexity of the clinical examination in MFS and the relevant differential diagnoses, evaluation should be coordinated by a professional with extensive experience, such as a geneticist, cardiologist, or ophthalmologist. The diagnosis is based on a defined set of clinical criteria drawn up by an international panel of experts: revised Ghent nosology for the MFS (Table 702-1).

In the absence of a conclusive family history of MFS, the diagnosis can be established in 4 distinct scenarios:
1. Aortic root Z score ≥2 and ectopia lentis
2. Aortic root Z score ≥2 and a bona fide FBN1 mutation
3. Aortic root Z score ≥2 and a systemic score ≥7
4. Ectopia lentis and a bona fide FBN1 mutation known to cause aortic disease

In the absence of a family history of MFS, a diagnosis can be established in the presence of:
1. Ectopia lentis
2. A systemic score ≥7
3. Aortic root Z score ≥2 if older than 20 yr or >3 if younger than 20 yr

In the absence of a family history of MFS, alternative diagnoses include:
1. Ectopia lentis ± systemic score and FBN1 mutation not known to associate with aortic aneurysm or no FBN1 mutation = ectopia lentis syndrome
2. Aortic root Z score <2 and a systemic score ≥5 (with at least 1 skeletal feature) without ectopia lentis = MASS (mitral valve prolapse, myopia, borderline and nonprogressive aortic enlargement, and nonspecific skin and skeletal findings) phenotype
3. Mitral valve prolapse and aortic root Z score <2 and a systemic score <5 without ectopia lentis = mitral valve prolapse syndrome

**Table 702-1** Diagnostic Criteria for Marfan Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic root Z score ≥2</td>
<td>1</td>
</tr>
<tr>
<td>Ectopia lentis</td>
<td>1</td>
</tr>
<tr>
<td>Aortic root Z score ≥2 and a systemic score ≥7</td>
<td>2</td>
</tr>
<tr>
<td>Ectopia lentis and a bona fide FBN1 mutation known to cause aortic disease</td>
<td>3</td>
</tr>
</tbody>
</table>

*Denotes caveat that features suggestive of an alternative diagnosis must be excluded and appropriate alternative molecular testing should be performed.

**Table 702-2** Scoring of Systemic Features in Points

- Wrist and thumb sign = 3 (wrist or thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hind foot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced US:LS and increased arm:height and no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, down-sloping palpebral fissures, midface hypoplasia, retrognathia)
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1

Maximum total: 20 points; score ≥7 indicates systemic involvement.
2. The presence of aortic root dilation (Z score ≥2) or aortic dissection and the identification of a bona fide FBN1 mutation (Table 702-3) are sufficient to establish the diagnosis even if ectopia lentis is absent.

3. When aortic root dilation (an aortic root Z score ≥2) or aortic dissection is present, but ectopia lentis is absent and the FBN1 status is either unknown or negative, the diagnosis may be confirmed by the presence of sufficient systemic findings (a systemic score ≥7 points; see Table 702-2). However, features suggestive of an alternate diagnosis must be excluded and the appropriate alternative molecular testing should be performed.

4. In the presence of ectopia lentis, but absence of aortic root dilation or aortic dissection, an FBN1 mutation, which has previously been associated with aortic disease, is required before the diagnosis can be made. If the FBN1 mutation is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as isolated ectopia lentis syndrome.

Despite these diagnostic criteria, on occasion young (<20 yr) sporadic cases may not fit in 1 of the 4 proposed scenarios detailed above. If insufficient systemic features (systemic score <7) and/or borderline aortic root measurements (Z score <3) are present without documented evidence of a bona fide FBN1 mutation, the term nonspecific connective tissue disorder is recommended. In those instances when a FBN1 mutation is identified, the term potential MFS should be used instead.

In an individual with a positive family history of MFS (where a family member has been independently diagnosed using the above criteria), the diagnosis can be established in the presence of:

1. Ectopia lentis
2. A systemic score >7 points (see Table 702-1)
3. Aortic root dilation with Z score ≥2 in adults (≥20 yr old) or Z score ≥3 in individuals younger than 20 yr old

In the case of scenarios 2 and 3, features suggestive of an alternative diagnosis must again be excluded and appropriate alternative molecular testing should be performed.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of MFS includes disorders with aortic aneurysms (Loeys-Dietz syndrome, familial thoracic aortic aneurysm syndrome, Shprintzen-Goldberg syndrome); ectopia lentis (ectopia lentis syndrome, Weill-Marchesani syndrome, and homocystinuria) [see Chapter 85.3]); or systemic manifestations of MFS (congenital contractural arachnodactyly and MASS phenotype) (Table 702-4).

**Aortic Aneurysm Syndromes**

An important differential diagnosis is Loeys-Dietz syndrome (LDS), a systemic connective tissue disorder characterized by the triad of arterial tortuosity and aggressive aneurysm disease, hypertelorism, and bifid uvula or cleft palate, as well as many of the craniofacial and skeletal features found in MFS. The diagnosis may be classified into LDS type 1 or LDS type 2 depending on whether the mutant locus resides in the TGFBR1 or the TGFBR2 gene, which encode the type 1 or the type 2 TGF-β receptors respectively. Two new LDS variants have been described, LDS type 3 and LDS type 4, which are caused by heterozygous mutations in the genes encoding the TGF-β1 intracellular signaling molecule SMAD3 and the extracellular ligand TGF-β1, respectively. These new subtypes are also characterized by widespread arterial tortuosity and aneurysm disease, aortic dissection, as well as typical craniofacial and skeletal abnormalities. Patients with SMAD3 mutations also appear predisposed to early onset osteoarthritis and supraventricular arrhythmias. Distinguishing between MFS and the various LDS subtypes is important because aneurysms tend to dissect at younger ages and smaller dimensions in LDS patients, necessitating more aggressive management.

Like MFS, familial thoracic aortic aneurysm syndrome segregated as an autosomal dominant trait characterized aortic root aneurysm and dissection. Other systemic manifestations of MFS are typically absent and the disorder has reduced penetrance. Disease-causing heterozygous mutations have been identified in several genes with roles in the vascular smooth muscle contractile apparatus, including MYH11, ACTA2, and MYLK, which encode smooth muscle myosin heavy chain 11, vascular smooth muscle α-actin, and myosin light chain kinase. However, these genes only account for a fraction of cases of nonsyndromic familial thoracic aortic aneurysm. In most cases, the management principles that have been generated for MFS have proved effective for this form of familial aortic aneurysm.

**Shprintzen-Goldberg syndrome** is a systemic connective tissue disorder that includes virtually all the craniofacial, skeletal, skin and cardiovascular manifestations of MFS and LDS, with the additional findings of craniosynostosis, hydrocephalus, mental retardation and severe skeletal muscle hypotonia. The majority of cases are caused by heterozygous mutations in the SKT1 gene, which encodes an intracellular repressor of TGF-β signaling. Vascular involvement tends to be less prevalent and less severe when compared to MFS or LDS.

**Ectopia Lentes Syndromes**

Both ectopia lentis syndrome and Weill-Marchesani syndrome may also be caused by heterozygous mutations in FBN1. Compound heterozygous or homozygous mutations at a second locus, ADAMTSL4, have been shown to cause ectopia lentis associated with slightly younger age at diagnosis. Interestingly, the same FBN1 mutation produces classical MFS, ectopia lentis, and ectopia lentis combined with skin, but not cardiovascular, manifestations of MFS, suggesting that these presentations are part of a spectrum of clinical features of the same disease.

Weill-Marchesani syndrome is a systemic connective tissue disorder characterized by skin, skeletal, and ocular abnormalities, including microspherophakia, ectopia lentis, and myopia. Features inconsistent with the diagnosis of MFS include short stature and brachydactyly. As well as FBN1 mutations (type 2), the syndrome may be caused by homozygous or compound heterozygous mutations in ADAMTS10 (type 1) or homozygous mutations in LTB2 (type 3).

**Homocystinuria** is a metabolic disorder caused by homozygous or compound heterozygous mutations in the gene encoding cystathionine β-synthase, which leads to increases in both homocysteine and methionine. The clinical features of untreated homocystinuria include ectopia lentis and skeletal abnormalities resembling MFS. However, in contrast to MFS, affected persons often suffer from developmental delay, a predisposition to thromboembolic events, and a high incidence of coronary artery disease.
### Syndromes with Systemic Manifestations of Marfan Syndrome

**Congenital contractural arachnodactyly** is a connective tissue disorder caused by heterozygous mutations in the gene encoding fibrillin-2 (FBN2). There are a number of clinical features overlapping with MFS including dolichostenomelia, anterior chest deformity, scoliosis, joint contractures, and arachnodactyly, as well as some craniofacial malformations, including highly arched palate and retrognathia. In addition, both may suffer from severe cardiovascular abnormalities leading to premature death, but the specific cardiac anomalies are quite different; valvular insufficiency and aortic root dilation in MFS whereas congenital heart defects are more common in congenital contractural arachnodactyly. Patients with congenital contractural arachnodactyly also suffer from crumpled auricular helices (a hallmark of this condition).

Many patients referred for possible MFS are found to have evidence of a systemic connective tissue disorder, including long limbs, deformity of the thoracic cage, striae atrophicae, mitral valve prolapse, and borderline but nonprogressive dilation of the aortic root, but do not meet diagnostic criteria for MFS. This constellation of features is referred to by the acronym MASS phenotype (mitral valve prolapse, myopia, borderline and nonprogressive aortic enlargement, and non-specific skin and skeletal findings). The MASS phenotype can segregate in large pedigrees and remain stable over time. The diagnosis is particularly challenging in the context of a young, sporadic patient in whom careful follow-up is needed to distinguish MASS phenotype from emerging MFS. Familial mitral valve prolapse syndrome can also be caused by mutations in the gene encoding fibrillin-1 and include subdiagnostic systemic manifestations.

### LABORATORY FINDINGS

Laboratory studies should document a negative urinary cyanide nitroprusside test or specific amino acid studies to exclude cystathionine β-synthase deficiency (homocystinuria). Although it is estimated that most, if not all, people with classic MFS have an FBN1 mutation, the large size of this gene and the extreme allelic heterogeneity in MFS have frustrated efficient molecular diagnosis. The yield of mutation screening varies based on technique and clinical presentation. It

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### Table 702-4 Differential Diagnosis of Marfan Syndrome

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Cardiac Features</th>
<th>Vascular Features</th>
<th>Systemic Features</th>
</tr>
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<tbody>
<tr>
<td><strong>AORTIC ANEURYSM SYNDROMES</strong></td>
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<tr>
<td>Loeys-Dietz syndrome (MIM 609192)</td>
<td>Patent ductus arteriosus</td>
<td>Aortic root aneurysm</td>
<td>Hypertelorism</td>
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<tr>
<td></td>
<td>Atrial septal defect</td>
<td>Arterial tortuosity</td>
<td>Cleft palate</td>
</tr>
<tr>
<td></td>
<td>Bicuspid aortic valve</td>
<td>Widespread aneurysms</td>
<td>Broad or bifid uvula</td>
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<tr>
<td></td>
<td></td>
<td>Vascular dissection at relatively young ages and small aortic dimensions</td>
<td>Craniosynostosis</td>
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<td>Midface hypertelorism</td>
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<td>Blue sclerae</td>
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<td></td>
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<td>Pectus deformity</td>
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<td>Scoliosis</td>
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<td>Joint hypermobility</td>
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<td>Pes planus</td>
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<td>Rarely</td>
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<td>Easy bruising</td>
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<td>Dystrophic scars</td>
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<td>Translucent skin</td>
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<td></td>
<td></td>
<td>Rarely developmental delay</td>
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<td></td>
<td></td>
<td></td>
<td>Generally none</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rarely livedo reticularis and iris flocculi</td>
</tr>
<tr>
<td>Familial thoracic aortic aneurysm (MIM 132900)</td>
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<td>Aortic root aneurysm</td>
<td>Hypertelorism</td>
</tr>
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<td>Shprintzen-Goldberg syndrome (MIM 182212)</td>
<td>Rare forms with patent ductus arteriosus</td>
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<tr>
<td></td>
<td>None</td>
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<td>Bicuspid aortic valve with aortic aneurysm (MIM: 109730)</td>
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<td>Ehlers-Danlos syndrome, type IV (MIM: 130050)</td>
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<td>Aneurysm and rupture of any medium to large muscular artery</td>
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<tr>
<td></td>
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<td>No predisposition for aortic root enlargement</td>
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<td><strong>ECTOPIA LENTIS SYNDROMES</strong></td>
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<tr>
<td>Familial ectopia lentis (MIM 129600)</td>
<td>None</td>
<td>None</td>
<td>Nonspecific skeletal features</td>
</tr>
<tr>
<td>Homocystinuria (MIM 236200)</td>
<td>Mitral valve prolapse</td>
<td>Intravascular thrombosis</td>
<td>Tall stature</td>
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<td></td>
<td></td>
<td></td>
<td>Ectopia lentis</td>
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<td></td>
<td></td>
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<td>Long-bone overgrowth</td>
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<tr>
<td><strong>SYNDROMES WITH SYSTEMIC MANIFESTATIONS OF MFS</strong></td>
<td></td>
<td>Borderline or nonprogressive</td>
<td>Nonspecific skin and skeletal findings</td>
</tr>
<tr>
<td>MASS phenotype (MIM 604308)</td>
<td>Mitral valve prolapse</td>
<td></td>
<td>Myopia</td>
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</table>
remains unclear whether the “missing” mutations are simply atypical in character or location within FBN1 or located in another gene. Other differential diagnoses, such as MASS phenotype, ectopia lentis, Weill-Marchesani syndrome, and Shprintzen-Goldberg syndrome, are associated with mutations in the FBN1 gene. It is often difficult or impossible to predict the phenotype from the nature or location of a FBN1 mutation in MFS. Hence, molecular genetic techniques can contribute to the diagnosis, but they do not substitute for comprehensive clinical evaluation and follow-up. The absence or presence of an FBN1 mutation is not sufficient to exclude or establish the diagnosis, respectively.

**MANAGEMENT**

Management focuses on preventing complications and genetic counseling. Referral to a multidisciplinary center where a geneticist with experience in MFS works in concert with subspecialists to coordinate a rational approach to monitoring and treatment is advisable given the complex nature of some patient’s disease. Yearly evaluations for cardiovascular disease, scoliosis, or ophthalmologic problems are imperative.

**CURRENT THERAPIES**

Most therapies currently available or under investigation aim to diminish cardiovascular complications, which can be categorized into activity restrictions, aortic surgery, endocarditis prophylaxis, and current pharmacologic approaches.

**Activity Restrictions**

Physical therapy can improve cardiovascular performance, neuromuscular tone, and psychosocial health, and so aerobic exertion in moderation is recommended. However, strenuous physical exertion, competitive or contact sports and particularly isometric activities, which invoke a Valsalva maneuver, such as weight lifting, should be avoided.

**Aortic Surgery**

Surgical outcome is more favorable if undertaken on an elective rather than an urgent or emergent basis (mortality of 1.5% vs 2.6% and 11.7%, respectively). Therefore, aortic surgery should be recommended for adult patients when their aortic root diameter approaches 50 mm, and early intervention considered for those with a rapid rate of enlargement (>5-10 mm per year) or a family history of early aortic dissection. There are no definitive criteria guiding the timing of surgery in children in whom dissection is extremely rare, irrespective of aortic size. This has prompted many centers to adopt the adult criterion of 50 mm, although early surgery may be undertaken in the presence of a rapid rate of growth (>10 mm per year) or the emergence of significant aortic regurgitation. Preserving the native aortic valve at the time of repair is desirable to avoid the need for lifelong anticoagulation. Replacement of the aortic root with a pulmonary root autograft (a Ross procedure) is not recommended as the neoaorta can undergo progressive enlargement and autograft failure once exposed to the systemic blood pressure. Mitral valve repair or replacement is advised for severe mitral valve regurgitation with associated symptoms or progressive left ventricular dilation or dysfunction.

**Pregnancy**

There is higher risk of aortic dissection during pregnancy in women with MFS. However, improved awareness and more recent analyses have indicated the risk is low in patients with an aortic root diameter <40 mm. Prophylactic aortic root replacement can minimize the risk of aortic dissection and death in women with MFS who wish to become pregnant.

**Endocarditis Prophylaxis**

The American Heart Association no longer recommends the use of antibiotic prophylaxis for persons with structural or valvular heart disease, but exceptions are made for select groups at the greatest risk for bad outcomes from infectious endocarditis. The Professional Advisory Board of the National Marfan Foundation believes that patients with MFS should continue to receive prophylaxis for bacterial endocarditis, in part because it remains unknown, but possible, that the myxomatous valves typical of MFS are a preferred substrate for bacterial infection.

**Current Pharmacologic Approaches**

β-Blockers have traditionally been considered the standard of care in MFS and multiple small observational studies suggest there is a protective effect on aortic root growth, with the dose typically titrated to achieve a resting heart rate <100 beats/min during submaximal exercise. Given the putative role of hemodynamic stress in aortic dilation and aortic dissection in MFS, these effects are attributed to the negative inotropic and chronotropic effects of β-blockade.

**EMERGING THERAPEUTIC STRATEGIES**

**Angiotensin II Receptor Type 1 Blockers**

There is extensive evidence linking angiotensin II signaling to TGF-β activation and signaling. In a mouse model of MFS, the angiotensin II receptor type 1 blocker losartan completely prevents pathologic aortic root growth and normalizes both aortic wall thickness and architecture. In support of its relevance to humans, a retrospective study assessing the effect of angiotensin II receptor type 1 blockers in a small cohort of pediatric patients with MFS who had severe aortic root enlargement despite previous alternate medical therapy, showed that angiotensin II receptor type 1 blockers significantly slowed the rate of aortic root and sinotubular junction dilation (both of which occur in MFS), whereas the distal ascending aorta (which does not normally become dilated in MFS) remained unaffected. Further evidence of a beneficial effect from losartan therapy is provided by 3 prospective clinical trials that demonstrated that losartan treatment alone or in combination with β-blockade slows the progression of aortic root dilation in patients with MFS. Nonetheless when compared to atenolol, losartan therapy in children and young adults with Marfan syndrome and aortic root dilatation demonstrated equivalent rates of aortic root dilation during a 3-yr study.

**PROGNOSIS**

The major cause of mortality is aortic root dilation, dissection, and rupture, with the majority of fatal events occurring in the 3rd and 4th decade of life. A reevaluation of life expectancy in MFS suggests that early diagnosis and refined medical and surgical management has greatly improved the prognosis for patients with the condition. Nevertheless, MFS continues to be associated with significant morbidity and selected subgroups are refractory to therapy and continue to show early mortality. In a review of 54 patients diagnosed during infancy, 89% had serious cardiac pathology; cardiac disease was progressive despite standard care (22% died during childhood, 16% before age 1 yr). In the more classic form of MFS, it is estimated that more than 90% of individuals will have a cardiovascular event during their lifetime, placing both physical and mental stresses on patients and their families. Awareness of these issues and referral for support services can facilitate a positive perspective toward the condition.

**GENETIC COUNSELING**

The heritable nature of MFS makes recurrence risk (genetic) counseling mandatory. Fathers of these sporadic cases are, on average, 7-10 yr older than fathers in the general population. This paternal age effect suggests that these cases represent new dominant mutations with minimal recurrence risk to the future offspring of the normal parents. Owing to rare reports of gonadal mosaicism in a phenotypically normal parent, the recurrence risk for parents of a sporadic case can be reported as low, but not zero. Each child of an affected parent, however, has a 50% risk of inheriting the MFS mutation and thus being affected. Recurrence risk counseling is best accomplished by professionals with expertise in the issues surrounding the disorder.

*Bibliography is available at Expert Consult.*
Bone growth occurs in children by the process of calcification of the cartilage. Bone growth is an acceleration of bone growth (length) of the limbs during prepubescence, and increased growth (length) of the trunk (spine) during early adolescence, and increased bone (length) of the limbs during prepubescence. The growth pattern of bones is an acceleration of bone growth and mineralization of cartilage, including growth hormone acting through insulin-like growth factors, thyroid hormones, insulin, leptin, ghrelin, and androgens and estrogens during the pubertal growth spurt. Supraphysiologic concentrations of glucocorticoids impair cartilage function and bone growth and augment bone resorption.

Rates of bone formation are coordinated with alterations in mineral metabolism in both the intestine and kidneys, where a number of hormones regulate the processes. Inadequate dietary intake or intestinal absorption of calcium causes a fall in serum levels of calcium and its ionized fraction. This serves as the signal for PTH synthesis and secretion, resulting in greater bone resorption (which raises the serum calcium level), enhanced distal tubular reabsorption of calcium, and promotes higher rates of renal synthesis of 1,25(OH)D3 or calcitriol, the most active metabolite of vitamin D (Fig. 703-1). Calcium homeostasis thus is controlled by the intestine because the availability of 1,25(OH)2D ultimately determines the fraction of ingested calcium that is absorbed.

Phosphate homeostasis is regulated by the kidneys because intestinal phosphate absorption is nearly complete and renal excretion determines the serum level of phosphate. Excessive intestinal phosphate absorption causes a fall in serum levels of ionized calcium and a rise in PTH secretion, resulting in phosphaturia, thus lowering the serum phosphate level and permitting the calcium level to rise. Hypophosphatemia blocks PTH secretion and promotes renal 1,25-dihydroxyvitamin D [1,25(OH)2D] synthesis. This latter compound also promotes greater intestinal phosphate absorption. The important role of FGF23 in phosphate homeostasis is described below.

Vitamin D can be synthesized in the skin under the influence of UV irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D3 (vitamin D3) in the liver and then further converted by the kidney. The enzyme cytochrome P450 (CYP) 27B converts 25(OH)D3 to 1α,25-(OH)2D3. 1,25(OH)2D3 binds to vitamin D receptor (VDR), which, after transport to the nucleus, acts to induce the transcription of more than 200 proteins. The functions of some of the proteins are indicated. VDR activation leads to productions of fibroblast growth factor 23 (FGF23). FGF23 induces phosphaturia (not shown), upregulates CYP 24, and downregulates CYP 27B.

Other hormones also appear to regulate the growth and mineralization of cartilage, including growth hormone acting through insulin-like growth factors, thyroid hormones, insulin, leptin, ghrelin, and androgens and estrogens during the pubertal growth spurt. Supraphysiologic concentrations of glucocorticoids impair cartilage function and bone growth and augment bone resorption.

Figure 703-1 Vitamin D metabolism. Vitamin D can be synthesized in the skin under the influence of UV irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D3 (vitamin D3) in the liver and then further converted by the kidney. The enzyme cytochrome P450 (CYP) 27B converts 25(OH)D3 to 1α,25-(OH)2D3. 1,25(OH)2D3 binds to vitamin D receptor (VDR), which, after transport to the nucleus, acts to induce the transcription of more than 200 proteins. The functions of some of the proteins are indicated. VDR activation leads to productions of fibroblast growth factor 23 (FGF23). FGF23 induces phosphaturia (not shown), upregulates CYP 24, and downregulates CYP 27B.
Vitamin D also can enter the metabolic pathway by ingestion of dietary vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol), both of which are absorbed from the intestine because of the action of bile salts. After absorption, ingested vitamin D is transported by chylomicrons to the liver, where, along with skin-derived vitamin D₃, it is converted to 25-hydroxyvitamin D [25(OH)D] by the action of a hepatic microsomal enzyme requiring oxygen, nicotinamide adenine dinucleotide phosphate, and magnesium to hydroxylate vitamin D at the 25th carbon atom. The 25(OH)D is next transported by DBP to the kidneys, where it undergoes further metabolism. 25(OH)D is the main circulating vitamin D metabolite in humans (Table 703-1).

Because the synthesis of 25(OH)D is weakly regulated by feedback, its plasma level rises in summer and falls in winter. High vitamin D intake raises the plasma level of 25(OH)D to many times above normal, but the parent vitamin D compound itself is absorbed by adipose tissue.

In the kidneys, 25(OH)D undergoes further hydroxylation, depending on the prevailing serum concentration of calcium, phosphate, PTH and FGF23. If the calcium or phosphate level is reduced or the PTH level is elevated, the enzyme 25(OH)D-1-hydroxylase is activated and 1,25(OH)₂D is formed. The enzyme cytochrome P450 (CYP) 27B1 converts 25(OH)D to 1α,25-(OH)₂D. 1,25(OH)₂D binds to vitamin D receptor, which, after transport to the nucleus, acts to induce the transcription of 200–400 proteins and peptides. The functions of some of the proteins are known.

Another class of proteins important in the regulation of mineral balance and vitamin D synthesis are the phosphatonin. Among these are FGF23, sFRP-4 (secreted Frizzled-related protein 4), and MEEPE (matrix extracellular phosphoglycoprotein). Overexpression of FGF23 results in hypophosphatemia, phosphaturia, reduced serum 1,25(OH)₂D values, and some forms of disorders. Disorders of phosphate balance, including hyper- and hypophosphatemia, can relate to loss or gain of function of these phosphatonin (see Fig. 703-1).

Vitamin D receptor activation by 1,25(OH)₂D leads to production of FGF23. FGF23 is produced by osteocytes and targets another organ, the kidney, to promote phosphaturia. FGF23 reduces expression/insertion of 2 sodium phosphate transporters into the renal proximal tubule, resulting in higher levels of urinary phosphate excretion. This bone-derived hormone also inhibits renal hydroxylase activity (CYP 27B1) and promotes 24-hydroxylase activity. Consequently, circulating 1,25(OH)₂D levels fall.

A gene termed Klotho codes for a single-pass transmembrane protein that is an aging suppressor in mice. Klotho protein also influences interaction of FGF23 with its receptor FGF23R. FGF23 is then able to inhibit the action of CYP27B1 and the sodium-dependent phosphate transporter in the kidney. The net result of Klotho FGF23 interaction is reduced 1,25(OH)₂D values and phosphaturia.

The active metabolite, 1,25(OH)₂D, circulates at a level that is only 0.1% of the level of 25(OH)D (see Table 703-1) and acts on the intestine to increase the active transport of calcium and stimulate phosphate absorption. Because 1α-hydroxylase is a mitochondrial enzyme that is tightly feedback regulated, the synthesis of 1,25(OH)₂D declines after serum calcium or phosphate values return to normal. Excessive 1,25(OH)₂D is converted to an inactive metabolite. In the presence of normal or elevated serum calcium or phosphate concentrations, the renal 25(OH)D-24-hydroxylase is activated, producing 24,25-dihydroxyvitamin D [24,25(OH)₂D], which is a pathway for the removal of excess vitamin D; serum levels of 24,25(OH)₂D (1-5 ng/mL) increase after ingestion of large amounts of vitamin D (see Fig. 703-1), or in the presence of increased concentrations of FGF23.

Although hypervitaminosis D and production of inactive metabolites can occur after oral dosing, extensive skin exposure to sunlight does not usually produce toxic levels of 25(OH)D, suggesting natural regulation of the production of this metabolite in cutaneous tissue. Serum 1,25(OH)₂D levels are higher in children than in adults; not as subject to seasonal variability, and peak in the 1st yr of life and again during the adolescent growth spurt. These values must be interpreted in light of the prevailing serum calcium, phosphate, and PTH values, and with regard to the entire vitamin D metabolite profile.

Mineral deficiency prevents the normal process of bone mineral deposition. If mineral deficiency occurs at the growth plate, growth slows and bone age is retarded, a condition called rickets. Poor mineralization of trabecular bone resulting in a greater proportion of unmineralized osteoid is the condition of osteomalacia. Rickets is found only in growing children before fusion of the epiphyses, whereas osteomalacia is present at all ages. All patients with rickets have osteomalacia, but not all patients with osteomalacia have rickets. These conditions should not be confused with osteoporosis, a condition of equal loss of bone volume and mineral (see Chapter 707).

Rickets may be classified as calcium-deficient or phosphate-deficient rickets. Because both calcium and phosphate ions constitute bone mineral, the insufficiency of either type in the extracellular fluid that bathes the mineralizing surface of bone results in rickets and osteomalacia. The 2 types of rickets are distinguishable by their clinical manifestations (Table 703-2). Rickets can also occur in the face of mineral deficiency, despite adequate vitamin D stores. True dietary calcium deficiency rickets is found in some parts of Africa but rarely in North America or Europe. A form of phosphate-deficiency rickets can occur in infants given prolonged administration of phosphate-sequestering aluminum salts as a treatment for colic or gastroesophageal reflux. This results in the phosphate depletion syndrome.

Bibliography is available at Expert Consult.
Bibliography
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AD, autosomal dominant; AR, autosomal recessive; E, elevated; L, low; N, normal; V, variable; XL, X-linked; Y, yes.
Skeletal dysplasias are classified under 3 major categories: osteodysplasias, chondrodysplasias, and dysostoses. The osteodysplasias affect bone density and often lead to osteopenia. The chondrodysplasias are genetic disorders of cartilage and result in deficient linear growth. The dysostoses affect a single bone.

In primary chondrodystrophy, which is an autosomal dominant condition, bowing of the legs, short stature, and a waddling gait appear in the absence of abnormalities of serum levels of calcium and phosphate, alkaline phosphatase activity, or vitamin D metabolites. Metaphyseal chondrodysplasia (Jansen type) is very rare and is typified by cupped and ragged metaphyses, which develop mottled calcification at the distal ends of bone over time (Fig. 704-1). Hypercalcemia, with serum values of 13-15 mg/dL, can occur. The spine can also be deformed by the irregular growth of vertebrae. Three different mutations, resulting in ligand independent activation, have been identified in parathyroid hormone receptor type I as the molecular cause of this syndrome, as have some of the downstream target genes that can contribute to the pathogenesis of the disease. The Schmid type of metaphyseal chondrodysplasia is less severe, although the radiographic appearance of the knees and extreme bowing of the lower limbs resemble signs seen in patients with familial hypophosphatemia. It is associated with defects in collagen type X, alpha 1, and the hip abnormalities are more debilitating than in Jansen metaphyseal chondrodysplasia. Patients with both types of metaphyseal chondrodysplasia have lifelong short stature.
Metaphyseal dysostosis, or Pyle disease, results from defects in endochondral bone formation and metaphyseal modeling. The long ends of bones are splayed, resulting in an “Erlenmeyer flask” defect. Short stature is not necessarily characteristic, and serum chemical levels are normal. Leonine features often develop if the facial bones are involved. Metaphyseal dysostosis may also be a clinical feature of Shwachman-Diamond syndrome, a rare autosomal recessive disorder characterized by neutropenia, pancreatic exocrine insufficiency, bone marrow dysfunction, and sometimes severe hematologic complications (see Chapter 448). Allogeneic bone marrow transplantation has been used as a therapeutic approach, with mixed results.

There are no other currently available forms of treatment known to be effective for the chondrodystrophies or dysostosis.

Bibliography is available at Expert Consult.
Bibliography


Hypophosphatasia, which radiographically resembles rickets, is defined by low serum alkaline phosphatase activity and mainly affects the skeleton and teeth. This inherited disorder (with both autosomal recessive and dominant forms) is an inborn error of metabolism in which activity of the tissue-nonspecific (liver, bone, kidney) alkaline phosphatase isoenzyme (TNSALP) is deficient, although activity of the intestinal and placental isoenzymes is normal. Single-point mutations of the gene prevent expression of the activity of this enzyme in vitro and indicate its necessity for normal skeletal mineralization. A large proportion of the more than 100 mutations of the gene identified to date are missense mutations, although splice-site mutations, small deletions, and frameshift mutations also have been found. The only phenotype associated with these mutations is hypophosphatasia. Some patients have a regulatory defect involving this enzyme rather than a mutation.

There is considerable heterogeneity in the severity of the disease and 6 forms of the condition are described. Some cases appear at birth, and diagnosis has even been made in utero by radiographic examination of a fetus. The disease can appear in a lethal neonatal or perinatal form (congenital lethal hypophosphatasia), a severe infantile form, or a milder form occurring in childhood or late adolescence (hypophosphatasia tarda) (Fig. 705-1). The lethal form is characterized by a moth-eaten appearance at the ends of the long bones, severe deficiency of ossification throughout the skeleton, and marked shortening of the long bones. Patients with mild disease can present with bowing of the legs and variable statural shortening. Hypercalcemia is common in the neonatal and infantile forms, and because calcium accumulation by mature chondrocytes does not occur, patients might appear to have rickets.

Unusual clinical manifestations include wormian bones in the calvariae; poor calcification of the frontal, parietal, and occipital bones; and premature loss of deciduous or permanent teeth, due to hypoplasia of dental cementum. Because of the hypercalcemia in the infantile form, nephrocalcinosis is also found.

In the childhood form, bone pain, frequent fractures, and milder skeletal deformities are evident, as well as premature tooth loss. The metaphyseal defect consists of irregular ossification, punched-out areas, and metaphyseal cupping.

There is an adult form, manifesting in middle age, which is characterized by recurrent metaphyseal stress fractures and femoral pseudo-fractures. The lethal and infantile forms are autosomal recessive. The milder forms can be either autosomal recessive or dominant.

In hypophosphatasia, large quantities of phosphoethanolamine are found in the urine because this compound cannot be degraded in the absence of TNSALP activity. Plasma inorganic pyrophosphate and pyridoxal-5-phosphate levels are also elevated for the same reason. Pyridoxal-5-phosphate levels tend to be lower than normal in most
other bone diseases and hence can aid in the differential diagnosis of hypophosphatasia. Seizures in patients with the lethal and infantile forms of the disease may be related to impaired pyridoxine metabolism. Although no satisfactory therapy has been found, infusion of plasma rich in alkaline phosphatase activity has been helpful in healing bone in short-term studies. Enzyme replacement therapy with recombinant human TNSALP improves skeletal healing and mineral content, pulmonary status, and overall physical activity. Bone marrow transplantation has been successful using donors with normal TNSALP values. The clinical course of this condition often improves spontaneously as an affected child matures, although early death from renal failure or flail chest leading to pneumonia can occur in the severe infantile form of the disorder.

Rare patients presenting with identical clinical and radiographic patterns have normal serum alkaline phosphatase activity. Their disease has been labeled pseudohypophosphatasia and might represent the presence of a mutant alkaline phosphatase isoenzyme that reacts to artificial substrates in an alkaline environment (in a test tube) but not in vivo with natural substrates.

*Bibliography is available at Expert Consult.*
Bibliography

Hyperphosphatasia is defined by excessive elevation of the bone isoenzyme of alkaline phosphatase in serum and significant growth failure. Osteoid proliferation in the subperiosteal portion of bone results in separation of the periosteum from the bone cortex. Bowing and thickening of the diaphyses are common, along with osteopenia (Fig. 706-1). The disease usually has its onset by 2-3 yr of age, when painful deformity developing in the extremities leads to abnormal gait and sometimes fractures. Other common findings include pectus carinatum, kyphoscoliosis, and rib fraying. The skull is large, and the cranium is thickened (widened diploë) and may be deformed. Skull involvement can lead to progressive and profound hearing loss. Radiographically, the bony texture is variable; dense areas (showing a teased cotton-wool appearance) are interspersed with radiolucent areas and general demineralization. Long bones appear cylindrical, lose metaphyseal modeling, and contain pseudocysts that show a dense, bony halo. There exist several clinical phenotypes.

In this autosomal recessive disorder, serum levels of both calcium and phosphate are normal, whereas urinary leucine amino acid peptidase activity and serum acid phosphatase levels are increased. This disorder is often called juvenile Paget disease because, as in adult-onset Paget disease, calcitonin can reduce the rapid bone turnover found in this disorder; in children, the disorder is more generalized and symmetric. This disorder is distinct from Paget disease because histology of bone reveals a lack of normal cortical bone remodeling and an absence of the classic mosaic pattern of lamellar bone found in the adult condition. Hence, the term juvenile Paget disease is inappropriate. A case has been reported in which intense intravenous bisphosphonate (ibandronate) therapy administered over a 3 yr period arrested progression of idiopathic hyperphosphatasia, preventing deformity and disability and improving hearing.

Transient hyperphosphatasia occurs between 2 mo and 2 yr of age, has no associated manifestations other than some mild gastrointestinal symptoms; it is usually detected during routine (screening) laboratory evaluation for some unrelated complaint. Liver and bone isoenzyme fractions are elevated; there are no other manifestations of hepatic or bone dysfunction. Serum alkaline phosphatase values as high as 3,000-6,000 IU/L may be encountered. The cause is unknown. Resolution usually occurs within 4-6 mo.

Familial hyperphosphatemia, an autosomal dominant trait, is another benign condition that is distinguished from the transient infantile form by persistent and asymptomatic elevations of serum alkaline phosphatase levels.

A more serious autosomal dominant variant, expansile skeletal hyperplasia, is characterized by early-onset deafness, premature loss of teeth, progressive hyperostotic widening of long bones causing painful phalanges in the hands, episodic hypercalcemia, and enhanced bone

**Figure 706-1** Hyperphosphatasia showing bowing and thickening of the diaphyses and osteopenia. (From Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 167-26, p. 2744.)
remodeling. A defect in the gene that encodes receptor activation of nuclear factor γB is relevant. This gene appears to be necessary for osteogenesis, and the defect leads to increased activity of nuclear factor γB in the skeleton.

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


Osteoporosis, the most common bone disorder in adults, is relatively uncommon in children. This disorder is characterized by diminished bone volume and a marked increase in the prevalence of fractures. In contrast to osteomalacia, which shows undermineralization and normal bone volume, histologic sections of bone in all forms of osteoporosis reveal a normal degree of mineralization but a reduction in the volume of bone, especially trabecular bone (vertebral bone). There is a reduction in trabecular bone turnover as well. In osteoporosis, by definition, there is a reduced amount of bone tissue (termed osteopenia), which is associated with atraumatic (pathologic) fractures. Osteoporosis in children may be primary or secondary (Table 707-1). The primary osteoporoses can be divided into heritable disorders of connective tissue, including osteogenesis imperfecta (see Chapter 701), Bruck syndrome, osteoporosis-pseudoglioma syndrome, Ehlers-Danlos syndrome (see Chapter 659), Marfan syndrome (see Chapter 702), homocystinuria, and idiopathic juvenile osteoporosis. Secondary forms of osteoporosis include various neuromuscular disorders, chronic illness, endocrine disorders, and drug-induced and inborn errors of metabolism, including lysinuric protein intolerance and Gaucher disease.

When no obvious primary or secondary cause can be detected, idiopathic juvenile osteoporosis should be considered, especially if the following clinical features are evident: onset before puberty, long-bone and lower back pain, vertebral fractures, long-bone and metatarsal fractures, a washed-out appearance of the spine and appendicular skeleton, and improvement after puberty. Trabecular bones such as the spine and metatarsals are particularly affected by atraumatic fractures.

In general, blood values of minerals, vitamin D metabolites, alkaline phosphatase, and parathyroid hormone are normal. Evaluation of bone mineral content and bone density by dual-energy x-ray absorptiometry or, less often, quantitative CT shows markedly reduced values. Several modes of therapy (including oral calcium supplements, calcitriol, bisphosphonates, and calcitonin) have been used with some success in individual conditions, but the effect of these treatments is difficult to gauge because spontaneous recovery occurs after the onset of puberty in more than 75% of cases.

**Table 707-1** Risks for Osteoporosis

<table>
<thead>
<tr>
<th>ENDOCRINE DISORDERS</th>
<th>CONNECTIVE TISSUE/BONE DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Hypogonadism</td>
<td>Juvenile osteoporosis</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea (athletic</td>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>triad)</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Homocystinuria</td>
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<tr>
<td>Premature and primary ovarian</td>
<td>Fibrous dysplasia</td>
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<tr>
<td>failure</td>
<td></td>
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<tr>
<td>Depot medroxyprogesterone acetate</td>
<td></td>
</tr>
<tr>
<td>therapy</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor α (ESR1)</td>
<td>Previous or recurrent low impact fractures</td>
</tr>
<tr>
<td>mutations</td>
<td>Early onset osteoporosis with WNT1 mutations</td>
</tr>
<tr>
<td>Male Hypogonadism</td>
<td>X-linked osteoporosis with fractures with PLS3</td>
</tr>
<tr>
<td>Primary gonadal failure (Klinefe</td>
<td>mutatons</td>
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<tr>
<td>lter syndrome)</td>
<td></td>
</tr>
<tr>
<td>Secondary gonadal failure</td>
<td>DRUGS</td>
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<tr>
<td>(idiopathic hypogonadotropic</td>
<td>Alcohol</td>
</tr>
<tr>
<td>hypogonadism)</td>
<td>Heparin</td>
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<tr>
<td>Delayed puberty</td>
<td>Glucocorticosteroids</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Thyroxine</td>
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<tr>
<td>Hyperparathyroidism</td>
<td>Anticonvulsants</td>
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<tr>
<td>Hypercortisolism (therapeutic or</td>
<td>Gonadotropin-releasing hormone agonists</td>
</tr>
<tr>
<td>Cushing disease)</td>
<td></td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>Cyclosporine</td>
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<tr>
<td>Thyrotoxicosis</td>
<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Cigarettes</td>
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<td>INFLAMMATORY DISORDERS</td>
<td>MISCELLANEOUS DISORDERS</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Immobilization (cerebral palsy, spinal muscular</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>atrophy, Duchenne dystrophy)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Malabsorption syndromes (cystic</td>
<td>Glycogen storage disease type 1</td>
</tr>
<tr>
<td>fibrosis, celiac disease, biliary</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>atresia)</td>
<td>Low calcium dietary intake</td>
</tr>
<tr>
<td>True or perceived milk intolerance</td>
<td>Gaucher disease</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>Severe congenital neutropenia</td>
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<tr>
<td>Chronic obstructive jaundice</td>
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<tr>
<td>Primary biliary cirrhosis and</td>
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<td>other cirrhoses</td>
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<td>Alactasia</td>
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<td>Subtotal gastrectomy</td>
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<td>BONE MARROW DISORDERS</td>
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<tr>
<td>Bone marrow transplant</td>
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<td>Lymphoma</td>
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<td>Leukemia</td>
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<tr>
<td>Hemolytic anemias (sickle cell</td>
<td></td>
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<tr>
<td>anemia, thalassemia)</td>
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<tr>
<td>Systemic mastocytosis</td>
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</table>
Bone and Joint Disorders

mapped to chromosome 11q12-13. The mutation is a loss of function in the gene for low-density lipoprotein receptor-related protein 5. Interestingly, gain-of-function mutations result in a gene product that increases bone density.

The life-cycle implications of either significant demineralization or osteoporosis in childhood need to be stressed. Events in childhood influence peak bone mass, and late adolescence is a period of rapid bone mineral accretion. Peak bone mass is achieved by 20-35 yr of age (depending on the bone measured), and the contribution during childhood is considerable. A number of measures influence bone mass: vitamin D (400-800 IU daily), calcium intake (≥1,200 mg/day in adolescents), and weightbearing exercise throughout childhood. Weight-bearing exercise enhances bone formation and reduces bone resorption. Other factors that can prevent acquisition of peak bone mass include use of alcohol and tobacco. Excellent sources of dietary calcium include mainly dairy products but also bony fish, green vegetables, and calcium-supplemented drinks (e.g., orange juice). Yogurt and cheeses can be used in lactase-deficient children. Because it appears that adult-onset osteoporosis is the result of a number of genetic factors, thus forming a complex trait interaction, specific interventions during childhood to influence bone mass are not available.

The treatment of secondary osteoporosis is best achieved by treating the underlying disorder when feasible. Hypogonadism should be treated with hormone replacement therapy, especially in thin athletic women (see Chapter 691). Calcium intake should be increased to 1,500-2,000 mg/day. In glucocorticoid-induced osteoporosis, an emphasis on the lowest possible dose to prevent disease activity (inflammatory bowel disease) with alternate-day or topical therapy and the use of inhaled glucocorticoids in asthma is essential. Special diets for inborn errors of metabolism are also appropriate. Celiac disease may be overrepresented in adults with osteoporosis and should be screened for and treated appropriately (see Chapter 338.2). Treatment with bisphosphonates that inhibit bone resorption in certain secondary (glucocorticoid-induced) and adult-onset osteoporosis has been successful. Bisphosphonate therapy is also beneficial in osteogenesis imperfecta and cerebral palsy.

Bibliography is available at Expert Consult.
Bibliography


Pediatric rehabilitative medicine is dedicated to improving the lives and daily function of children with acute and chronic disabilities and to maximizing their potential. It is based on an understanding of the importance of early intervention among those children identified as needing or potentially needing additional support; the development of simpler, culturally relevant surveillance systems that function well in all nations and within all populations within nations; and expanding intervention programs in the scope of services offered and reach of programs.

EPIDEMIOLOGY
The Centers for Disease Control estimates that the prevalence of developmental disabilities in the United States increased by 17% between 1997-1999 and 2006-2008 (Table 708-1). Over the past 3 decades, mortality rates have plummeted among children in lower- and middle-income nations (see Chapter 1). A least a portion of those who formerly would not have survived early childhood have disabilities; it is estimated that more than 200 million children from lower- and middle-income nations have developmental delays or disabilities.

APPROACH
Rehabilitation requires knowledge of the enabling/disabling process and the interrelationships of pathology, impairment, functional ability, and social participation, superimposed on normal development. Rehabilitation management of children with impairments requires the integration and identification of their functional capabilities and selection of the best rehabilitation intervention strategies. A well-designed rehabilitation program can reverse many disabling conditions and can help patients cope with deficits that cannot be reversed by medical care. The goal of rehabilitation is to maximize an individual’s function and participation in society.

Pediatric rehabilitation medicine uses an interdisciplinary approach to address the prevention, diagnosis, treatment, and management of congenital and childhood-onset impairments, including related or secondary medical, physical, functional, cognitive, psychosocial, and vocational limitations or conditions, with an understanding of the life course of the disability. It requires identifying and managing common pediatric rehabilitation medical conditions and complications, including nutrition, bowel management, bladder management, gastrointestinal reflex, skin protection, pulmonary hygiene and protection, sensory impairments, sleep disorders, spasticity, swallowing dysfunction, and behavioral problems.

Therapeutic treatment includes (1) early intervention, (2) age-appropriate functional training, (3) programs of therapy, (4) play, (5) therapeutic exercise, (6) electrical stimulation and other modalities, (7) communication strategies, (8) oral motor interventions, (9) educational and vocational planning, (10) transitional planning, (11) adjustment to disability support, and (12) prevention strategies.

SCHEMA OF PRACTICE
Rehabilitation management of common pediatric problems includes musculoskeletal disorders and trauma, cerebral palsy, spinal dysraphism and other congenital anomalies, spinal cord injury, traumatic and other acquired brain injuries (see Chapter 710), limb deficiency/amputation, neuromuscular disorders, peripheral nerve injuries, and spasticity management.

A significant deleterious effect of childhood disability is inactivity. This is defined as a reduced functional capacity of musculoskeletal and other body systems. It should be considered a distinct diagnosis from the original condition that has led to a curtailment of normal physical function. The main adverse effects are muscle atrophy and weakness, joint contracture, and immobilization osteoporosis.

PREVENTION OF MUSCLE WEAKNESS
Muscle weakness can be reduced by prescribing progressive resistance, stretching, and aerobic exercises. A minimum of once-a-day muscle contraction at 30-50% of maximal strength for 3-5 min, 3 times per wk for a single muscle group, may suffice to prevent muscle loss and weakness. For chronic disuse atrophy with weakness and stiffness, strengthening and stretching exercises may be required for many months, and even then, the child is unlikely to gain normal strength and range of motion.

Stretching to maintain optimal muscle resting length as well as viscoelastic properties is important for maintaining muscle function. Muscles that cross 2 joints, such as the hamstrings, gastrocnemius, biceps, and long back extensor muscles, are particularly prone to stiffness. Once a contracture has developed, the treatment is active and passive range-of-motion exercises combined with a sustained terminal stretch on a daily basis. The daily stretching can prevent the loss of sarcomeres in series of immobilized muscles and maintain elongation properties of muscle fibers and surrounding connective tissue, maintaining range of motion.

Stretching techniques include ballistic, static, or passive and neuromuscular facilitation. Prevention of injury and treatment of specific joint injury, as well as the presence and effects of pain or muscle spasms, require modification. The intensity should be a mild degree of tightness without discomfort. Static stretches are held 15-60 sec. Passive and neuromuscular facilitation is a 6 sec contraction followed by 10-30 sec of assisted stretch. Stretching is generally more successful when used in combination with the application of deep heat (i.e., ultrasound). Sustained stretching lasting 2 hr can be obtained by splinting (orthotics, serial casting). In patients with spasticity, chemical denervation (botulinum toxin, phenol blocks) may improve positioning inside the cast or orthotic to improve the tolerance for wearing.

Dynamic splinting provides tension in the desired direction with the use of springs or elastic bands. This type of splinting is often used in the hand and arm because it allows a measure of function while providing stretching. To achieve optimal joint position, it is sometimes necessary to surgically lengthen the contracted tendon.

Maintenance of skeletal mass depends largely on mechanical loading applied to the bone by muscle pull and the force of gravity. Bone mass only increases with repeated loading and increase in muscle strength. Disuse osteoporosis can be prevented by regular use of isotonic exercises, weight bearing, and functional training. Passive loading and standing are of little benefit.

A variety of therapeutic exercise techniques have been developed to address central nervous system dysfunction. Most commonly used are neurodevelopmental techniques using reflex inhibitory patterns to inhibit increased tone along with advanced postural reactions to stimulate recovery. Other therapeutic programs include proprioceptive neuromuscular facilitation. There is no convincing evidence that any...
of these methods actually alter the natural history of recovery. These approaches to therapy seem to be most useful in enabling the child to develop compensatory techniques. Using these methods, patients improve performance in and gain independence with such tasks as making transfers, stretching, bed mobility, and safe ambulation.

**OTHER ASSIST DEVICES**
Rehabilitation often includes prescribing age-appropriate assistive devices and technology to assist environmental accessibility, including orthotics, prosthetics, wheelchairs, positioning, activities of daily living aids, interfaces and environmental controls, and augmentative communication devices. The goal of all assistive devices is to overcome the limitations and improve function and community participation.

Rehabilitation management of children with developmental or acquired disabilities is best accomplished through a medical home and team approach seeking to maximize the child's level of motor, intellectual, emotional, and social functioning.

*Bibliography is available at Expert Consult.*
Bibliography


A rehabilitation evaluation starts with determining physiologic impairments and strengths. The strengths may turn out to be pivotal in how well the individual compensates for his or her actual impairments. Physiologic impairments are the biologic shortfalls, which limit the child. Many assessment tools are available and professional organizations have developed compendiums of such tools.

The assessment begins with cognitive issues. Where is the child in the developmental spectrum in language, social, and emotional abilities? How does the child function in the family, school, and community? Does the presence of an impairment act as an impediment to social acceptance? Poor impulse control, stuttering, or speaking loudly, perhaps because of hearing loss, will all distance a child from other children of the same age group.

Sensory issues need to be evaluated. Are vision, hearing, and other senses present and meeting the needs of the child? Impairment of the sense of touch and position sense may affect the child's extremity function, particularly in the area of fine motor activities. Deficiencies in these skills can also affect how others perceive the child.

For a child who has significant disabilities, the evaluation team needs to include educators, neuropsychologists, social workers, physical therapists, occupational therapists, speech therapists, augmentative communication and device technicians, and seating and adaptive equipment specialists, as well as the physician. The pediatric rehabilitation evaluation is a process that not only looks at the actual impairments but looks to see how they affect the functioning of the individual. Functional substitutions and adaptive equipment and strategies need to be applied by the team to minimize the overall impact of the child's impairments on the child's function, maturation, and separation from family and, ultimately, on the child's function as an adult.

Upper-extremity function is assessed to determine strength, range of motion, and agility. Obviously, weakness of both the arms and legs will result in a greater degree of dysfunction than weakness of only the arms or only the legs. Lower-extremity function affects movement in other environments as well.

For one child, a manual wheelchair may enhance mobility. But children with arm weakness may need electric wheelchairs, with their associated complications. Problems of accessibility, transport, and cost can become significant issues for the family. Fine motor and prehension (the highly complex motor and sensory tasks performed by the hand) tasks are closely assessed because some of these children may need to rely on their ability to interface with access joysticks and computers and strength in these areas may compensate for physical weaknesses.

Skeletal deformities, range-of-motion limitations, and contractures may affect gross motor function, balance, sitting, walking, and climbing. Scoliosis, kyphosis, and pelvic obliquity may limit sitting balance and tolerance, which can secondarily affect upper-extremity function and the amount of time a child is able to socialize.

FAMILY CHARACTERISTICS

The education, vocation, and mental well-being of the parents or caregivers have a dramatic impact on the child. We know that if a child with impairment is to reach maximum potential, a stable and loving family structure facilitates the child's outcome. Does the family have other stressors, such as illness, death, divorce, and legal problems? What are their health care resources?

THE PHYSICAL ENVIRONMENT

Environment assessment begins with the child's room and home. Access to and inside the home should be discussed. How is this child transported? If the child uses power mobility, does the chair travel with the child or does it need to reside at the school or home or elsewhere? How is the child mobile in environments in which the power chair is not available? Is the transport of the child the problem? What is the adequacy, cost, and reliability of the van that is being used by the family? How the child gets in and out of the wheelchair is a significant part of the evaluation. Does the child assist with this, or is the child totally and passively dependent on an adult to move the child from, for example, a toilet seat back to the wheelchair?

In the school, does the child have access to all of the building and can the child participate in all activities in the building, such as those in the art and music rooms, cafeteria, science lab, and stage? Does the
child participate in clubs, teams, and other activities outside of the home?

**THE PREVIOUSLY HEALTHY CHILD**
For children who have established themselves in the general community and functioned in their environment in a normal capacity but then acquire a significant impairment, it becomes incredibly important to understand what their world looked like before they were affected by this new set of problems. If the child is old enough to remember what life had been like, the loss of function can be devastating. Coping with “what could have been” coupled with what was lost will require the help of skilled psychosocial clinicians.
Medical rehabilitation is an integral part of the process of assisting families and their children in transitioning from acute medical care after a severe traumatic brain injury (TBI) to reintegration into the community. Table 710-1 lists the quality of care indicators for inpatient pediatric TBI rehabilitation based on a review of evidence and the application of the RAND/UCLA modified Delphi Method.

**ETIOLOGY**
The cause of TBI varies by age. For young children, ages 0-4 yr, falls and nonaccidental trauma are the most common causes. The major cause of TBI among adolescents >14 yr is motor vehicle traffic. TBI is more common in males than females at all ages.

**PATHOPHYSIOLOGY**
Brain injury from trauma results from a combination of primary and secondary injury. The mechanism of injury can be different in children because of factors that differentiate them from adults; very young children have open sutures, so they can accommodate some increase in intracranial pressure by an increase in their head circumference or widening of the sutures. Compared with adults, children also have a larger head size compared to their neck musculature, higher brain water content, and less myelination, all of which are thought to contribute to greater brain distortion with resultant injury.

**ACUTE REHABILITATION**
The acute rehabilitation course for children with severe TBI includes addressing multiple medical issues related to the injury in addition to the provision of rehabilitation services. One of these issues is the possibility of seizure activity. Although it is common practice to initiate prophylactic anticonvulsant therapy early after injury, it is appropriate to consider discontinuing this treatment if late seizures have not occurred. Among children, early seizures do not correlate with the later development of epilepsy. The severity of injury, the presence of severe edema, and a very young age at injury increase the likelihood of the later development of posttraumatic seizures.

Sleep disturbance is common after TBI and can have an effect on the individual’s ability to function (Fig. 710-1). Various approaches, including sleep hygiene, sleep aids, strategic stimulants, cognitive behavioral therapy, strategic caffeine, and naps, can be tried for both the initiation and maintenance of sleep. Other chronotherapy techniques (coordinating the biologic rhythms of a child’s body with his/her medical therapy) may be necessary to address sleep–wake cycle abnormalities.

Children with severe TBI may also experience autonomic dysfunction characterized by elevated temperature, heart rate, respiratory rate, and blood pressure, accompanied by diaphoresis and posturing. Autonomic dysfunction is a diagnosis of exclusion and is associated with poor outcome after acquired brain injury in children. Autonomic dysfunction develops in approximately 13% of children with acquired brain injury, 10% of those with TBI, and 31% of those with injury as a result of cardiac arrest. Autonomic dysfunction is associated with longer hospital lengths of stay and poorer outcomes.

Acute inpatient rehabilitation emphasizes functional goals and community reintegration. The child and family are integral members of the rehabilitation team. Community reintegration involves careful consultation and planning with the school system to facilitate the transition from hospital to school. In the United States, federal law requires that a physician document that a child had a TBI to qualify for special education services under this disability category. Rehabilitation team consultation with the school team is essential for participation in school is essential for peer interaction and a step toward normalization of the child’s life. Schools can adapt to the child’s needs rather than providing services in an isolating homebound manner.
OUTCOMES ASSOCIATED WITH SEVERE
TRAUMATIC BRAIN INJURY
The most disabling consequences of TBI are cognitive, particularly
those associated with executive function.

In severe TBI, cognition is often the most affected area of functioning
and outcomes are associated with preinjury adaptive functioning and
family function. Attentional skills may remain impaired in children
10 yr after sustaining a TBI. Subsets of attention appear to be more
impaired after TBI, particularly divided and sustained attention.

Other areas of long-term impairment of cognitive performance
after pediatric TBI include overall intellectual performance, learning,
metamemory, working memory, social competence, and a variety of
behavioral concerns. Impairments have been noted in ability to
perform self-care activities, communicate, and participate in commu-
nity and social activities.

PEDIATRIC TRAUMATIC BRAIN INJURY
AND PLASTICITY
In the past there has been an assumption that sustaining a TBI at a
young age compared to more advanced age would allow for better
outcomes because of plasticity. In fact, plasticity may actually be related
to poorer outcomes in those injured at a very young age. The major
task of childhood is development and learning; a significant TBI can
impact the child's ability to learn. Likewise, children do not have over-
learned material to fall back on as do adults. There is some evidence
that the anticipated changes associated with brain maturation, includ-
ing cortical thinning of specific regions, do not occur in children who
have had TBI at a young age. There are potentially critical periods in
development during which a child is more at risk for the effects of a
brain injury. Because children are expected to develop cognitive skills
over time, the full extent of the impairment from injury might not be
recognized until a significant amount of time has elapsed following
the injury. For example, if executive function were impaired, one
wouldn't expect to see the manifestations of that until adolescence.

Bibliography is available at Expert Consult.
Chapter 710  ◆  Severe Traumatic Brain Injury  3400.e1

Bibliography


Chapter 711
Spinal Cord Injury and Autonomic Crisis Management
David W. Pruitt and Mary A. McMahon

EVALUATION
The most accurate way to assess a patient who has sustained a spinal cord injury (SCI) is by performing a standardized physical examination as endorsed by the International Standards for Neurological and Functional Classification of Spinal Cord Injury (Fig. 711-1). These standards provide the basic definitions of the terms utilized by clinicians caring for patients with SCI. Caution is recommended in utilizing and trusting the anorectal examination portion of this examination in children and youth because of poor interrater reliability.

CLINICAL MANIFESTATIONS
Children with neurologic levels of injury at T6 or above are particularly at risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, autonomic dysreflexia (AD). Children and adolescents with cervical and upper level SCI have lower baseline blood pressure compared with the general population. Blood pressure elevations of 20-40 mm Hg above baseline may be considered a sign of AD. AD is a sustained sympathetic response in relation to a noxious stimulus below the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of skin above the level of injury. Noxious stimuli are most often localized to bladder or rectal distention, but may include a number of other causes (Table 711-1). Identification and treatment of the noxious stimulus is

<table>
<thead>
<tr>
<th>Table 711-1</th>
<th>Potential Etiologies of Noxious Stimuli Causing Autonomic Dysreflexia</th>
</tr>
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</table>
| Urinary System | • Bladder distention  
• Bladder or kidney stones  
• Blocked/kinked catheter  
• Detrusor sphincter dyssynergia  
• Urinary tract infection  
• Urologic instrumentation  
• Shock wave lithotripsy |
| Gastrointestinal System | • Bowel distention  
• Bowel impaction  
• Gallstones  
• Appendicitis  
• Gastric ulcers  
• Gastritis  
• Gastrointestinal instrumentation  
• Hemorrhoids |
| Integumentary System | • Constrictive clothing, shoes, or orthotics  
• Blisters  
• Burns, sunburn, or frostbite  
• Ingrown toenail  
• Insect bites  
• Pressure ulcers |
| Musculoskeletal System | • Fractures  
• Heterotopic ossification  
• Functional electrical stimulation |
| Reproductive System–Male | • Epididymitis  
• Scrotal compression (sitting on scrotum)  
• Sexual intercourse  
• Sexually transmitted infections |
| Reproductive System–Female | • Menstruation  
• Pregnancy, especially labor and delivery  
• Vaginitis  
• Sexual intercourse  
• Sexually transmitted infections |
| Hematologic System | • Deep vein thrombosis  
• Pulmonary embolus |
| Other Systemic Causes | • Boosting (an episode of autonomic dysreflexia intentionally caused by an athlete with spinal cord injury in an attempt to enhance physical performance).  
• Excessive alcohol intake  
• Excessive caffeine or diuretic intake  
• Over-the-counter or prescribed stimulants  
• Substance abuse |

typically associated with resolution of symptoms without the use of antihypertensive medication. If necessary, antihypertensive agents with a rapid onset and short duration, including nifedipine and nitropaste, are advocated (Fig. 711-2). Emergent management of AD is necessary owing to the risk of cerebrovascular accident and additional organ damage as a result of sustained hypertension.

Deep venous thrombosis and pulmonary embolism are common, potentially life-threatening conditions in patients with SCI. In children and youth, deep venous thromboses are more common in postpubertal children. Prophylactic treatment, including low-molecular-weight heparin and calf compression pumps, during acute rehabilitation is recommended. Late-occurring deep venous thrombosis most commonly occurs with increased immobilization related to illness or surgery and prophylactic measures should be considered during these situations as well.

Following SCI, the bladder can be areflexic or hyperreflexic and detrusor sphincter dyssynergia is possible. Clean intermittent catheterization is typically used 4-6 times/day to keep bladder volumes below capacity. Anticholinergic medications can improve bladder storage. Asymptomatic bacteriuria, without vesicoureteral reflux, is generally not treated.

Bowel continence requires optimal consistency through the use of diet and medications and planned evacuation, employing aids including gastrocolic reflex, digital stimulation, suppositories, and enemas. Individuals with SCI have increased risk for dysphagia, delayed gastric emptying, ileus, gastric ulceration, pancreatitis, and superior mesenteric artery syndrome.

Frequent monitoring for skin breakdown and pressure ulcers is necessary both acutely as well as lifelong in individuals with SCI. Common locations include the occiput, elbows, sacrum, ischium, and heels. Devices such as halo vests and splints increase risk. Frequent inspection and repositioning are important means of minimizing risk.

Depending upon the level of the lesion, paralysis of the diaphragm or intercostal and abdominal muscles can result in restrictive ventilatory impairment and ineffective cough. Respiratory muscle training, abdominal binders, and noninvasive ventilation and airway clearance devices, such as the insufflator-exsufflator cough assist device, should be considered in select patients.

Immediately following SCI there is a period of spinal shock with low tone and absent reflexes. Eventually, signs of an upper motor neuron lesion will increase, including spasticity and involuntary muscle spasms. Symptoms typically increase with noxious stimulation and can interfere with sleep, comfort, positioning, and care. Management includes pharmacologic therapy, stretching, splinting, and positioning. Focal spasticity can be treated with chemodenervation using botulinum toxin or phenol. Intrathecal baclofen should be considered for severe generalized spasticity.

Increased bone resorption occurs as a result of immobilization. If excessive calcium is not adequately excreted by the kidneys, insidious onset of abdominal pain, nausea, vomiting, lethargy, polydipsia, and polyuria may occur. This immobilization hypercalcemia is managed with intravenous fluid hydration at 1.5-2 times the maintenance rate, as well as use of furosemide to hasten the renal excretion of calcium. Complications include nephrocalcinosis, urolithiasis, and renal failure.

Osteopenia begins immediately after an SCI occurs and plateaus 6-12 mo later. Pathologic fractures occur as a consequence of loss of bone mineral density. The most common sites of fracture include the supracondylar region of the femur and the proximal tibia; fracture is often associated with gait training, minor trauma, and range of motion. Treatment should include use of removable splints or casts that are well padded over bony prominences to prevent skin breakdown. Prevention through weight bearing and calcium and vitamin D supplementation is encouraged.

Development of spine deformity and scoliosis is prevalent in patients sustaining SCI prior to puberty and many of these individuals will require surgical correction. Because of the high incidence of scoliosis, radiographs of the thoracolumbar-sacral spine should be obtained every 6 mo prior to skeletal maturity and every 12 mo thereafter.

An SCI will impact the child's social-emotional development, so adjustment should be monitored closely. Positive coping strategies and strong social supports are associated with greater social participation. Education regarding sexual development and function with SCI injury should be provided.

**PROGNOSIS**

Prognosis for recovery of neurologic deficits resulting from SCI depends on the neurologic level of injury and level of completeness. Examination at least 72 hr after injury has been determined a better indicator of the prognosis than examinations done earlier. It is prudent for those determining and communicating the diagnosis to understand the particularities and limitations of the anorectal examinations, and thus completeness of injury, unique to children. Those individuals with incomplete injury tend to have increased likelihood of neurologic recovery. The neurologic level of injury can be assistive in determining the level of independence with functional activities (Table 711-2).

*Bibliography is available at Expert Consult.*
Bibliography
Table 711-2 Projected Functional Outcomes at 1 Yr after Injury and/or Diagnosis According to Neurologic Level of Injury

<table>
<thead>
<tr>
<th>Activity</th>
<th>C1-C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8-T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding</td>
<td>Dependent</td>
<td>Independent with adaptive equipment after set-up</td>
<td>Independent with or without adaptive equipment</td>
<td>Independent</td>
<td>Independent</td>
</tr>
<tr>
<td>Grooming</td>
<td>Dependent</td>
<td>Minimal assistance with equipment after set-up</td>
<td>Some assistance to independent with adaptive equipment</td>
<td>Independent with adaptive equipment</td>
<td>Independent</td>
</tr>
<tr>
<td>Upper-extremity dressing</td>
<td>Dependent</td>
<td>Requires assistance</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
</tr>
<tr>
<td>Lower-extremity dressing</td>
<td>Dependent</td>
<td>Dependent</td>
<td>Requires assistance</td>
<td>Some assistance to independent with adaptive equipment</td>
<td>Usually independent</td>
</tr>
<tr>
<td>Bathing</td>
<td>Dependent</td>
<td>Dependent</td>
<td>Some assistance to independent with equipment</td>
<td>Some assistance to independent with equipment</td>
<td>Independent</td>
</tr>
<tr>
<td>Bed mobility</td>
<td>Dependent</td>
<td>Assistance</td>
<td>Assistance</td>
<td>Independent to some assistance</td>
<td>Independent</td>
</tr>
<tr>
<td>Weight shifts</td>
<td>Independent in power; dependent in manual wheelchair</td>
<td>Assistance unless in power wheelchair</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
</tr>
<tr>
<td>Transfers</td>
<td>Dependent</td>
<td>Maximum assistance</td>
<td>Some assistance to independence on level surfaces</td>
<td>Independence with or without board for level surfaces</td>
<td>Independent</td>
</tr>
<tr>
<td>Wheelchair propulsion</td>
<td>Independent in power; dependent with manual</td>
<td>Independent in power; dependent to some assistance in manual with adaptations on level surfaces</td>
<td>Independent–manual with coated rims on level surfaces</td>
<td>Independent–except curbs and uneven terrain</td>
<td>Independent</td>
</tr>
<tr>
<td>Driving</td>
<td>Unable</td>
<td>Independent with adaptations</td>
<td>Independent with adaptations</td>
<td>Car with hand controls or adapted van</td>
<td>Car with hand controls or adapted van</td>
</tr>
<tr>
<td>Activities of daily living (grooming, feeding, dressing, bathing)</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
</tr>
<tr>
<td>Bowel/bladder</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
<td></td>
</tr>
<tr>
<td>Transfers</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
<td>Independent</td>
<td></td>
</tr>
<tr>
<td>Ambulation</td>
<td>Standing in frame, tilt table, or standing wheelchair</td>
<td>Exercise only</td>
<td>Household ambulation with orthosis</td>
<td>Community ambulation is possible</td>
<td></td>
</tr>
</tbody>
</table>

Spasticity is a component of the upper motor neuron syndrome characterized by velocity-dependent resistance to passive range of motion resulting in tonic stretch reflexes and accompanied by exaggerated tendon jerks. Spasticity management is determining what degree of spasticity may be tolerable and of functional benefit vs counterproductive and potentially injurious. When devising a treatment plan, both the positive and negative effects of spasticity on function must be considered; treatment should maximize function while minimizing sedation and adverse effects.

### ORAL MEDICATIONS

Oral medications are often used as an early treatment for generalized spasticity (Table 712-1). Although efficacy of certain antispasmodics has been demonstrated, their use should be contingent upon functional benefit as adverse effects are quite common. Frequently used medications include baclofen, benzodiazepines (diazepam, clonazepam), dantrolene sodium, tizanidine, and clonidine.

#### GABAergic Medications

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system. The 2 most relevant GABA receptors for the purposes of pharmacologic management of spasticity are GABA_A and GABA_B. Benzodiazepine medications exert their effect through

<table>
<thead>
<tr>
<th>Table 712-1</th>
<th>Dosing Guidelines, Pharmacologic Actions, and Adverse Event Profile of Commonly Prescribed Oral Antispasmodic Medications for Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL MEDICATION (DOSE/FREQ., AGE/WEIGHT RANGE)</strong></td>
<td><strong>MODE OF ACTION</strong></td>
</tr>
<tr>
<td>Baclofen (0.125-1 mg/kg/day)</td>
<td>Centrally acting, structural analog of γ-aminobutyric acid (GABA), binds to GABA_A receptors of presynaptic excitatory interneurons (and postsynaptic primary afferents) causing presynaptic inhibition of monosynaptic/polysynaptic spinal reflexes. Rapid absorption, blood level peaks in 1 hr, half-life 5.5 hr. Rinal (70-80% unchanged) and hepatic (15%) excretion.</td>
</tr>
<tr>
<td>Diazepam (0.12-0.8 mg/kg/day)</td>
<td>Centrally acting; binds to GABA_A receptors mediating presynaptic inhibition in brainstem reticular formation and spinal polysynaptic pathways. Rapid absorption; blood level peaks in 1 hr, with half-life of 30-60 hr. Metabolized in liver, producing pharmacologically active metabolites with long duration of action. Increased potential for adverse effects with low albumin levels as a result of being 98% protein bound.</td>
</tr>
<tr>
<td>Dantrolene Sodium (3-12 mg/kg/day)</td>
<td>Peripheral action, blocking release of calcium from sarcoplasmic reticulum with uncoupling of nerve excitation and skeletal muscle contraction. Blood level peaks in 3-6 hr (active metabolite 4-8 hr), with half-life of approximately 15 hr. Metabolized largely in liver, with 15-25% of nonmetabolized drug excreted in urine.</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Centrally acting, α₂-adrenocceptor agonist activity at both spinal and supraspinal sites. Prevents release of excitatory amino acids, facilitating presynaptic inhibition. Good oral absorption, blood level peaks in 1-2 hr, with a half-life of 2.5 hr. Extensive first-pass hepatic metabolism with urinary excretion of inactive metabolites.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Centrally acting, mixed α-adrenocceptor agonist with predominant α₂ activity causing membrane hyperpolarization at multiple sites in brain, brainstem, and dorsal horns of spinal cord. Inhibition of substance P may also contribute to tone reduction via an antinociceptive effect. Rapidly absorbed orally, blood level peaks in 1-1.5 hr, with a half-life of 6-20 hr.</td>
</tr>
</tbody>
</table>
GABA<sub>3</sub> receptors by increasing the affinity of GABA for the GABA<sub>3</sub> receptor. This results in presynaptic inhibition and a net inhibitory effect at both spinal and supraspinal levels. Of the benzodiazepines, diazepam is the oldest and most commonly used medication to treat spasticity because of its long half-life and need for less-frequent administration. In children <2 yr of age, clonazepam is a good option because of the availability of a liquid formulation and dosing guidelines. The cognitive effects of benzodiazepines limit its use in persons with severe spasticity as dose escalation results in increased sedation. Furthermore, sedation and cognitive slowing limit the usefulness of benzodiazepines in persons with spasticity of cerebral origin as it may impede recovery in acquired brain injury and cognitive development in congenital developmental delay. The use of benzodiazepines may lead to physiologic dependence, and, thus, abrupt discontinuation should be avoided to prevent withdrawal.

**Baclofen** is a GABA<sub>B</sub> agonist and is a preferred agent in the treatment of spasticity of spinal origin. Baclofen exerts an inhibitory effect on both monosynaptic and polysynaptic spinal reflexes. Unfortunately, supraspinal receptor sites also exist, resulting in sedation, which is common to all GABAergic medications. In most instances, daytime dosing of oral baclofen is better tolerated than benzodiazepines with regard to sedation. Intrathecal administration of baclofen via a baclofen pump (see below) allows greater selectivity of spasticity reduction while minimizing adverse cognitive effects. Abrupt cessation of both oral and intrathecal baclofen therapy must be avoided as it may result in a life-threatening withdrawal response.

**α<sub>2</sub>-Adrenergic Agents**

Clonidine and tizanidine are examples of centrally acting α<sub>2</sub>-adrenergic agents that decrease spasticity and have an antinoceptive effect. Clonidine is the older of the 2 agents and is used more frequently as an antihypertensive agent. Clonidine exerts its effect on spasticity via both presynaptic inhibition of sensory afferents, as well as release of glutamate at the level of the spinal cord. Adverse effects of clonidine that limit its use as an antispasmodic include hypotension, bradycardia, sedation, cognitive impairment, and xerostomia.

**Tizanidine** is an α<sub>2</sub>-noradrenergic agonist that is as effective as diazepam and baclofen in tone reduction. In comparison to clonidine, tizanidine has less-potent hemodynamic effects, which is desirable when it is used primarily for spasticity reduction. The half-life of tizanidine is approximately 2.5 hr, requiring frequent dosing to maintain a steady state. Adverse effects of tizanidine include hypotension, sedation, xerostomia, dizziness, hallucination, and hepatotoxicity.

**Peripherally Acting Calcium Blockers**

Dantrolene sodium works at the level of skeletal muscle to block calcium release from the sarcoplasmic reticulum. Despite its peripheral site of action, dantrolene may induce sedation, although to a lesser degree than other centrally acting agents. Dantrolene is effective at decreasing both clonus and spasticity but achieves this by weakening skeletal muscle in a nonselective fashion. The resultant generalized weakness seen with dantrolene use limits its utility in ambulatory patients. Dantrolene has a rare but significant adverse event of fatal hepatotoxicity in less than 1% of patients. Hepatotoxicity risk increases with increasing age, increasing dose, and female sex.

Pediatric dosing of spasticity medications is quite variable and needs to be tailored to the response of the child. The choice of medication is often based on personal experience and the impact of benefit vs potential adverse effects. See Table 712-1 for dosing guidelines.

**Surgical Management**

Surgical management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative management. Combining treatment options such as injections and systemic medications can be very effective.

**Botulinum toxin (BTX) intramuscular injections** and **phenol/alcohol neurolysis** are used to treat focal areas of spasticity. These injections are most effective in children with hypertonia localized to specific muscles and those without significant contracture. BTX blocks signal transmission at the neuromuscular junction by preventing the release of acetylcholine from the presynaptic axon of the motor end plate. Treatment with BTX type A is most common but BTX type B is also used. The period of clinically useful relaxation is usually 12-16 wk and it is recommended that injections be spaced a minimum of 3 mo apart because of concern for neutralizing antibody formation. Adverse events related to BTX are rare and include injection-site pain and focal muscle weakness. The FDA requires black box labeling on BTX products cautioning that the effects of the BTX may spread from the area of injection to other areas of the body, causing symptoms similar to botulism. Co-administration of BTX and aminoglycosides or other agents interfering with neuromuscular transmission (curare-like non-depolarizing blockers, lincomedines, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should be performed with caution as the effect of the toxin may be potentiated. BTX-A is an effective and generally safe treatment for spasticity of the upper and lower extremities; evidence regarding functional improvement is conflicting. Long-term use of BTX-A with repeated rounds of injections in children with cerebral palsy is safe and efficacious. BTX-A injections into the gastrocnemius can be combined with serial casting to help improve ankle range and gait.

**Phenol** perineural injections are typically performed in the large proximal muscles (biceps brachii, hip adductors, hamstrings) and duration of clinical effect may be longer than BTX, varying between 3 and 18 mo. Phenol injection of the anterior branch of the obturator nerve in children with cerebral palsy is safe and effective. The low cost of phenol is a significant advantage over BTX, but the need for electrical stimulation guidance and general anesthesia may offset any cost savings. Combining phenol injections with BTX allows an increased number of affected muscles to be injected at the maximal recommended dose during one procedure. Phenol is safe in children, but transient sensory dysesthesias occur rarely.

**Intrathecal baclofen (ITB)** is highly effective in treating severe spasticity. ITB is delivered to the intrathecal space via a surgically implanted infusion pump and catheter. This method of delivery confers an advantage over enteral baclofen in that central nervous system depressive effects are minimized and dosages can be titrated to functional effect. A preoperative screening bolus dose of baclofen can be delivered via lumbar puncture and is used to evaluate responsiveness and impact on functional abilities. Goals of treatment, whether they are to improve function, comfort, and/or care, need to be firmly established. Cost and maintenance can be prohibitive for some families. Catheter tips are typically positioned at C5-T2 but can be placed intraventricularly for severe dystonia. ITB is effective in children with cerebral palsy; there may be a significant reduction in upper- and lower-extremity spasticity for up to 10 yr. Speech, communication, and salivary control can improve after ITB. The most frequent and serious adverse events related to device and implant procedures are catheter dislodgement from the intrathecal space, catheter break/cut, and implant site infection, including meningitis. Electromagnetic interference and MRI may cause transient operational changes to the pump and changes in flow rate. Although baclofen pumps do not prohibit MRI imaging, it is recommended that the pump be “interrogated” by a programmer after MRI as a precaution. ITB pumps need to be replaced every 5-7 yr for end of battery life. The pump comes in a 20 mL and 40 mL size, both of which measure 8.75 cm in diameter. The baclofen pump requires regular refills at 2-6 mo intervals depending on dose rate and pump size, and refills are readily performed in an outpatient clinic setting. **ITB withdrawal** is a medical emergency and needs to be identified early and managed aggressively. Sequelae can include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, can advance to rhabdomyolysis, multiple organ–system failure, and death. Prevention of abrupt discontinuation of ITB requires careful attention to programming and monitoring of the infusion system, refill scheduling, and pump alarms.

Caregivers need to be educated about the early symptoms of baclofen withdrawal.

**Selective dorsal rhizotomy (SDR)** is a surgical procedure that has been widely used as a treatment for spasticity. The surgical technique...
involves single-level or multilevel osteoplastic laminectomies exposing the L2-S1 nerve roots. Typically, 25-70% of dorsal rootlets are selectively cut with the aid of electrophysiologic monitoring. Children 3-8 yr of age with spastic diplegia, minimal upper-limb involvement, good selective motor skills and strength, and minimal contractures are the best candidates for SDR. The preoperative ability to rise from a squatted position with minimal support or a younger child's ability to crawl on hands and knees are positive predictors for a good outcome with SDR. Children must have the cognitive and social capacity for the requisite intensive postoperative therapy program. Long-term outcomes 5 and 20 yr after SDR in children show an improvement in spasticity, motor function, and gait pattern. SDR can reduce the need for orthopedic surgeries, with 35% of children avoiding surgery; this might be more likely if SDR is performed before the age of 5 yr. Long-term complications such as sensory dysfunction, bladder or bowel dysfunction, or back pain are infrequent. A concern with multilevel laminectomies is the potential increased risk of spinal deformities, but there is no clear evidence to support this.

Bibliography is available at Expert Consult.
Bibliography


Birth brachial plexus palsy (BBPP) may cause significant arm weakness and subsequent functional deficits in children. The nerves to the arm are affected with variable degrees of weakness and sensory loss. Most children will have good recovery spontaneously, but functional deficits will remain in 20-30% of children with BBPP (see Chapter 99.7).

The mechanism for birth brachial plexus injury appears to be a lateral stretch of the plexus for the vast majority of cases. Anatomic variations in bones, blood vessels, and tendons lead to a very small number of cases. The incidence of BBPP is reported as 0.5-4.6 per 1,000 live births, with variability thought to be attributable to the type of obstetric care and the size of infants around the world.

Risk factors for birth brachial plexus injury include prior infants with BBPP, shoulder dystocia, birthweight greater than 4 kg, multiparous mothers, mothers with excessive weight gain, and diabetic mothers. Delivering twins or triplets, as well as cesarean sections, have been described as protective from BBPP.

Nerve injuries include neurapraxia, neurotmesis, and axonotmesis. Neurapraxia is the least severe of these types and is a reversible loss of nerve conduction. This type will recover. Neurotmesis is the most severe and is a total and complete disruption of the nerve; an avulsion describes a rupture of a preganglionic lesion, and a rupture describes the same event in a postganglionic lesion. Axonotmesis is the intermediate form and the most difficult to delineate. There is disruption of the epineurium with variable injury to the axons (Fig. 713-1). Nerves are made of groups of fascicles, which, in turn, are made of groups of axons. This type of lesion contributes greatly to the diagnostic dilemma and difficulty in prediction of recovery.

The brachial plexus consists of the anterior primary rami, or roots, from C5, C6, C7, C8, and T1 (Fig. 713-2). The trunks of the brachial plexus consist of C5-C6 forming the upper trunk, C7 forming the middle trunk, and C8-T1 forming the lower trunk; each trunk has anterior and posterior divisions. The posterior cord is formed from the posterior division of each trunk. The medial cord comes from the anterior division of the lower trunk. The lateral cord is formed from the anterior divisions of the upper and middle trunks.

Evaluation of the roots, trunks, and cords from which the nerves arise helps determine the site of injury.

Erb palsy is generally described as the upper trunk or C5-6 palsy. It is by far the most common injury seen in birth brachial plexus injury, present in three fourths of infants. It also demonstrates the greatest recovery rate at >80% with a functional arm. Klumpke palsy, C8-T1, is extremely rare in BBPP, likely not occurring except in the case of anatomic variation. If a baby presents with a C8-T1 deficit, the baby most likely originally had a complete C5-T1 BBPP and then had recovery of the upper portion of the plexus. This can happen because C4, C5, C6, and sometimes C7 are protected coming out from the spinal cord, held in a gutter along the transverse processes by connective tissue, whereas C8 and T1 are not. The sensory fibers are also relatively protected compared to the motor fibers because the sensory fibers run together until outside of the spinal cord into the dorsal root ganglion where their cell bodies lie. The motor fibers have the cell bodies within the spinal cord and so are not as cohesive in their path. Therefore the sensory fibers may be spared while motor fibers show clinical deficits.

A C8-T1 deficit may also result from a spinal cord injury. Consequently, it is important to check for any other indications of spinal cord injury throughout the body. Consideration also must be given to the potential of an anatomic variation, such as an anomalous rib, that may actually cause a C8-T1 deficit alone.

Because various parts of the brachial plexus have different risks of injury, the clinical presentation can be quite variable, causing the diagnosis to be challenging. The phrenic nerve may also be involved with its innervation from C3, C4, and C5, with potential respiratory concerns.

Included in the differential diagnosis of an infant with an arm deficit is the possibility of a fracture of the humerus or clavicle, osteomyelitis, a tumor, or congenital varicella infection, all of which may lead to the limited ability to move the arm.

**PHYSICAL EXAMINATION**

The physical examination of the child begins with observation. Examination for sensation, particularly examining for sharp sensation, useful in its own right, will also frequently help with active motor evaluation in infants. Assessment of muscle stretch reflexes is important in that infants with a brachial plexus palsy will be areflexive or hyporeflexive in the involved arm. Evaluation of primitive reflexes, particularly the Moro reflex, is helpful as most of these infants will have C5-6 involvement and therefore the Moro may show shoulder abduction and elbow flexion on 1 side but not the involved side. Range-of-motion examination is critical. Deficits are commonly seen because of the imbalance of muscles that are active and those that are not. Shoulder adduction and internal rotation is a common position, as is elbow flexion, forearm pronation, and wrist and finger flexion. The size of the involved arm may also be smaller because of muscle atrophy and sometimes shorter length and smaller diameter of the bone. In children with very severe deficits, the arm may be cooler because of the sympathetic nervous system outflow at T1. Torticollis is commonly present and almost always with the face turned away from the involved arm.

Among older infants and children, compensatory movements of the arm may be noted. Common examples are use of trunk momentum to move (particularly to rotate) the proximal arm, hyperlordosis of the lumbar spine to position the arm more advantageously, use of the pectoralis muscle to flex the shoulder, and use of the knee to physically flex the elbow. Examination of the back for symmetry, along with the scapulae for winging, is also relevant. Having the older child manipulate buttons, snaps, or zippers, throw and catch a ball, and write, print, or color may be revealing.

**LABORATORY EXAMINATION**

Radiographic evaluation may be needed. Plain films can be viewed immediately if there is reason to consider clavicle or humerus fracture, infection, osteomyelitis, or tumor. Ultrasound shows the nerves and this is improving as technology advances. MRI and CT myelogram are used for evaluation of nerve roots and nerves.

Electrodiagnostic evaluation may also contribute to the diagnosis. Sensory nerve conduction studies are very useful in a child with severe
Anatomy of Peripheral Nerve

- Longitudinal vessels
- Compression
- Outer epineurium
- Inner epineurium
- Fascicle
- Nerve fiber bundles
- Traction

Epineurial coat provides some protection against compression. Spiral configuration of nerve fiber bundles within fascicles provides some protection from traction.

Nerve Fiber Types

- Myelinated nerve fiber
  - Schwann cell
  - Node of Ranvier
  - Nerve cell axon
  - Myelin sheath
  - Axonal transport
    - Microtubules within axoplasm allow transport of cell products (anterograde and retrograde).
  - Compression may inhibit axonal transport.
- Unmyelinated nerve fiber
  - Schwann cell
  - Nerve fibers

Schematic of the brachial plexus

- 3 roots (ventral rami of spinal nerves)
- 5 roots from C4
- Contribution from C4
- Contribution from T2
- 1st rib
- To longus colli and scalene muscles (C5, 6, 7, 8)
- 1st intercostal nerve
- Long thoracic nerve (C5, 6, 7)
- Medial pectoral nerve (C8, T1)
- Medial cutaneous nerve of arm (T1)
- Thoracodorsal (middle subscapular) nerve (C6, 7, 8)
- Lower subscapular nerve (C5, 6)
- Suprascapular nerve (C5, 6)
- To subclavius muscle (C5, 6)
- Lateral pectoral nerve (C5, 6, 7)
- Terminal branches
  - 3 trunks
    - 3 anterior divisions
      - 3 posterior divisions
        - Lateral pectoral nerve (C5, 6, 7)
- Musculocutaneous nerve (C5, 6, 7)
- Axillary nerve (C5, 6)
- Radial nerve (C5, 6, 7, 8, T1)
- Median nerve (C5, 6, 7, 8, T1)
- Ulnar nerve (C7, 8, T1)
- Inconstant contribution
injury who has insensate areas. Normal sensory response in areas where the child cannot feel indicates a preganglionic neurotmesis (avulsion). Motor nerve conduction studies are useful to check for continuity of nerve fibers to muscles that are weak or paralyzed. F waves are useful in evaluating proximally as these responses go from peripheral nerves to the spinal cord and back. Somatosensory evoked potentials are difficult to perform with infants because of motor artifact obliterating the responses with movement and are impractical because of overlapping responses to peripheral stimulation. These are used intraoperatively as stimulation can be performed on the nerve roots themselves to determine proximal continuity. Electromyography can show activation in muscles with paralysis or severe weakness. It is important that these studies be performed by someone who is experienced in the examinations of infants and young children, both for the most precise evaluation and the most comfortable experience for the youngster. There are changes in nerve conduction velocities that occur with age, distances are nonclassic for traditional studies, and electrode placement is challenging because of the very small hands and limbs.

**TREATMENT**

Treatment begins on initial evaluation with instruction to the parents for positioning and early stretching exercises to begin at 10-14 days of age. They are also told of the critical task of maintaining infant awareness of the involved arm, initially by manually mimicking activities with the affected arm that the baby performs with the contralateral arm. The parents also are informed of the higher risk of BBPP for future infants, and so the families are encouraged to speak with the obstetrician about optimal management in future deliveries.

The baby will start with occupational or physical therapy at approximately 2 wk of age. The therapist will evaluate the baby as described above. The therapist will reiterate the importance of maximizing the awareness of the involved arm and will teach range-of-motion exercises. The therapist will often do splinting, commonly for wrist extension in a baby with wrist-drop, and possibly extending the fingers and abducting the thumb as well. Over time other splinting needs may be evident. There may be a supinator strap used during the therapeutic activities to turn the arm from a pronated position to supination. Therapeutic taping may be done for supination, wrist extension, or, most commonly, for shoulder positioning to minimize an adducted, internally rotated posture. The family is instructed in a home exercise program to be carried out on a daily basis, including stretching exercises, strengthening as a child is able, positioning, and use of splints.

After a few months of age the child may be able to tolerate electrical stimulation. Electrical stimulation to the muscles minimizes atrophy and promotes increased size, and therefore strength, of muscle fibers. Specific parameters for its use have not yet been determined but a 20-30 min twice-daily program is effective. Electrical stimulation to the nerves remains an area of contention, with some maintaining that it improves recovery while others stating that it impairs it. There are also proponents of the use of constraint-induced movement training to increase the active use of the involved hand. This is useful for a short-term increase in active use of the arm but less certain are long-term improvements. Biofeedback has been used to attempt to retrain muscles in those with BBPP. Botulinum toxin injections are also used to help balance out muscles that are overpowering weak muscles to minimize contractures.

Functional assessments are not widely used in children with BBPP. Computer adaptive testing using selected items from large item banks relevant to the child’s function may provide a meaningful evaluation tool. Hand function was evaluated with testing of children with upper-plexus involvement compared to their contralateral hand; 80% of the children had significantly greater-than-predicted decreased performance from the opposite hand. This indicated the hand function is impaired even in children who only have upper-plexus involvement.

Secondary problems can increase the negative impact of functional deficits in children with BBPP. Contractures from imbalance due to muscle weakness or paralysis, including shoulder adduction and internal rotation, elbow flexion, forearm pronation, and wrist and finger flexion, are all seen and interfere with function. A decrease in growth of the affected arm in length and atrophy of muscles are often seen. Lack of awareness of the arm, sometimes called developmental disregard, in children can have a significant impact on active use of the arm, with functional loss as a consequence. Pain is not usually seen in birth brachial plexus as opposed to injuries, which occur later in life. Scapular winging can be problematic both socially and clinically. The change in child development overall can be problematic. Toddlers with sensory loss sometimes chew on their fingers, causing injury.

Because the shoulder joint develops as the infant and toddler grows, deficits frequently develop. Shoulder deformity is a common musculoskeletal complication of BBPP. Muscular imbalance across the developing shoulder results in deformity of the skeletally immature glenohumeral joint. The weakness of shoulder external rotation, combined with strong internal rotation, leads to this difficulty. There can be progressive glenohumeral dysplasia, with increased glenoid retroversion, humeral head flattening, and posterior subluxation of the humeral head. The natural history of this deformity is progression if left untreated. This leads to further functional limitations even with a strong hand. Treatment aims to minimize this progression. Treatment options include botulinum toxin injections, arthroscopic surgeries, release of contracture, muscular tendinous lengthening (frequently a subscapularis slide), tendon transfers (commonly transfer of the latisimus dorsi to increase external rotation and abduction strength), and derotational humeral osteotomy.

Infants who do not show satisfactory improvement in muscle strength are candidates for surgical intervention. Classically the lack of elbow flexion to three fifths or greater strength merits referral for nerve surgery. The specific criteria and timing remain under debate. Those with a complete brachial plexus palsy with a flaccid arm and lack of sensation are under consideration for surgery between 2 and 4 mo of age, and those with upper-plexus involvement are considered between 3 and 6 mo of age. The surgical strategy for complete palsy is early microsurgery with the focus first on hand reinnervation. If the shoulder and elbow have continued deficits later, they will undergo secondary musculos tendinous procedures.

Nerve transfers, nerve grafting, and neurolysis all are commonly performed. Intraoperative electrical nerve studies can help guide the procedure. The somatosensory evoked potentials and nerve conduction studies, both nerve-to-nerve and nerve-to-muscle, are commonly performed. These can assist in determining functional electrical continuity of nerve fibers. Nerve grafting is commonly performed using sural nerve fascicles, with several fascicles attached at each root level. For those with no intact nerve roots, intercostal nerve and other peripheral nerve transfers or grafts, or a cross C7 graft (from the contralateral plexus), may be performed.

Recovery of muscle function can occur with extremely varied nerve grafts and transfers providing innervation, showing the amazing adaptability of the body and its recuperative power. Postoperative improvement in hand and arm function has been shown to have a negative correlation with age at surgery, and therefore early intervention is recommended.

For older babies and children, muscle tendon and bony procedures are generally performed, sometimes combined with a peripheral nerve procedure. The Oberlin procedure, using a portion of the ulnar nerve to the musculocutaneous nerve, just as it enters the biceps, is a classic peripheral nerve procedure. The Steindler flexorplasty is sometimes used to obtain elbow flexion by moving the flexor and pronator muscles from the medial epicondyle to the more proximal humerus. A subscapularis release with latisimus dorsi transfer is commonly used for shoulder abduction and external rotation. Shoulder joint procedures are becoming more common. For those with very severe arm involvement, the gracilis is sometimes used by taking this muscle along with the nerve and vascular supply for transfer to the arm for elbow flexion and/or wrist extension. A derotational osteotomy of the humerus is an older procedure that is still performed for changing the position of the shoulder and arm.

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


See Chapters 687 and 693.
Meningomyelocele (Spina Bifida)

Pamela Wilson and Janet Stewart

See also Chapter 591.
Meningomyelocele, or spina bifida, is a congenital neural tube defect that results in the malformation of the spine and spinal cord. It is the second most common disability in children and can range from spina bifida occulta (see Chapter 591.2) to anencephaly (see Chapter 591.6).

ETIOLOGY
See Chapter 591.1.

PREVENTION
See Chapter 591.1.

PRENATAL SCREENING
Prenatal screening is recommended for all pregnant women to detect neural tube defect. A simple blood test is done in the 2nd trimester to evaluate α-fetoprotein, human chorionic gonadotropin, estriol, and inhibin. If a neural tube defect is present, the α-fetoprotein is often elevated and further screening using high-resolution ultrasound is indicated. Ultrasound may reveal not only a spinal defect but also abnormal brain development, including the lemon and banana signs. The lemon sign is related to the shape of the head, whereas the banana sign is associated with hindbrain herniation of the cerebellum into the foramen magnum. The importance in early identification allows families to plan for delivery and consider fetal interventions, mainly prenatal closure of the defect. The Management of Meningomyelocele trial studied the safety and efficacy of prenatal spinal defect closure and the results suggest that prenatal closure may decrease the need for a shunt and lower the incidence of severe Arnold–Chiari malformations along with improved motor outcomes. However, study data show an increased incidence of preterm delivery and a risk for uterine dehiscence.

CLINICAL IMPLICATIONS
Spina bifida is often a multisystem problem that is most frequently associated with central nervous system abnormalities. The neurologic lesion is assessed by the actual anatomic level and then neurologic or functional level. Lesions associated with spina bifida are often grouped together as thoracic, upper lumbar (L1-2), midlumbar (L3), lower lumbar (L4-5), and sacral. Based on this information 1 can make inferences on the functional capabilities of the child and answer pertinent questions during the initial encounters (Table 715-1). The most basic question all families ask is: “Will my child walk?”

The first issue that must be dealt with after delivery is closure of the back defect. This is generally done the 1st day of life. Once the back is closed the child will be monitored to see if hydrocephalus develops. Hydrocephalus is very common in spina bifida and is related to hindbrain herniation. Hydrocephalus may develop most rapidly in the 1st postnatal mo; ventricular dilation may precede a change in head circumference or signs of increased intracranial pressure. The occurrence of hydrocephalus has been noted to be anywhere from 77-95% and does appear to have an association with level of lesion. Treatment is placement of a ventricular shunt or endoscopic third ventriculostomy. The risk for shunt revision in the 1st 2 yr is 30-50%, which decreases to 10% after 2 yr.

Hindbrain herniation or the Chiari type II malformation is seen in 80-90% of individuals with myelomeningocele. The classic manifestations include caudal displacement of the cerebellum, pons, and medulla and elongation of the fourth ventricle. This can impede cerebrospinal fluid flow and is involved in the development of hydrocephalus. The Chiari II malformation is symptomatic (from brainstem herniation/compression) in approximately 20% of children. Respiratory symptoms may be seen at birth or develop in the 1st few mo. These include stridor, vocal cord dysfunction, and central or obstructive apnea. Swallowing and feeding problems may require gastrostomy tube placement. If the child has a symptomatic Chiari II malformation, surgical

<table>
<thead>
<tr>
<th>MOTOR LEVEL</th>
<th>CRITICAL MOTOR FUNCTION PRESENT</th>
<th>MOBILITY: SCHOOL AGE</th>
<th>RANGE: ADULT</th>
<th>ACTIVITY: ADOLESCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12</td>
<td>Totally paralyzed lower limbs</td>
<td>Standing brace, wheelchair</td>
<td>Wheelchair</td>
<td>Wheelchair, no ambulation</td>
</tr>
<tr>
<td>L1-2</td>
<td>Hip flexor muscles</td>
<td>Crutches, braces, wheelchair</td>
<td>Wheelchair, household ambulation</td>
<td>Wheelchair, nonfunctional ambulation</td>
</tr>
<tr>
<td>L3-4</td>
<td>Quadriceps muscles</td>
<td>Crutches, braces, household ambulation, wheelchair</td>
<td>Crutches, household ambulation, wheelchair</td>
<td>50% Wheelchair, household ambulation with crutches</td>
</tr>
<tr>
<td>L5</td>
<td>Medical hamstrings, anterior tibial muscles</td>
<td>Crutches, braces, community ambulation</td>
<td>Crutches, community ambulation with crutches</td>
<td>Community ambulation with crutches</td>
</tr>
<tr>
<td>S1</td>
<td>Lateral hamstring and peroneal muscles</td>
<td>Community ambulation</td>
<td>Community ambulation</td>
<td>Community ambulation 50% crutch or cane</td>
</tr>
<tr>
<td>S2-3</td>
<td>Mild loss of intrinsic foot muscles possible</td>
<td>Normal</td>
<td>Normal</td>
<td>Limited endurance because of late foot deformities</td>
</tr>
</tbody>
</table>

decompression is indicated. All children with spina bifida are at risk for **tethered cord syndrome**. After shunt malfunction, this is the second most common cause for neurologic decline. Clinical manifestations of tethered cord syndrome include any change in gait or bowel or bladder function, increasing scoliosis, back pain, or orthopedic changes. Surgical detethering procedures are indicated in those with neurologic decline but the success rate is variable.

The **orthopedic complications** of myelomingenogcele are common and have predictable patterns. The spine deformities include scoliosis, lordosis, and kyphosis (see Chapter 679). The development of scoliosis has an association with the neurologic level. Children with thoracic level defects have an 80-100% risk, whereas those with a sacral level are at very low risk. Spine deformities tend to increase more rapidly during growth and puberty. Treatment of scoliosis includes both nonsurgical and surgical options. Braces, such as thoracic-lumbar-sacral orthotics, therapy, and proper seating options may be beneficial. Surgically implanted growing rods to support the developing spine have been used in younger children. Spine surgery should definitely be considered if the scoliotic spine curvature reaches 45 degrees; the child who is nearing skeletal maturity is a better candidate for spine surgery. Realistic expectations need to be discussed with the child and family. Correction of the spine may improve sitting, posture, and pelvic obliquity, but may have a negative impact on function and ambulation.

The **development of the hip** is also influenced by neurologic level (see Chapter 678). The risk for dislocation is highest in the L3 level followed by the L1-L2. Unilateral hip dislocations should be fixed surgically as they may result in pelvic obliquity and problems with sitting, whereas bilateral dislocations generally do not require interventions. Contractures of soft tissues are commonly seen in children with higher lesion levels. Hip flexors and knee flexors are commonly involved. Abnormalities in the foot occur in approximately 90% of children and adolescents. The goal of treatment is to achieve a plantar grade foot for weight bearing and allow shoe wear. Clubfoot deformities are common in babies and treatment commonly includes serial casting and orthotics (see Chapter 674.3). The results are often suboptimal and surgery may be needed. In addition congenital vertical talus (rocker-bottom feet) are often encountered and need to be addressed (see Chapter 674.4).

**Osteoporosis** (see Chapter 707) begins to develop in childhood and is more severe in the higher-level injuries. Fractures of the lower extremities are most common in the femur followed by the tibia. Preventive treatment includes use of supplemental calcium and vitamin D. Those with documented fractures should undergo a diagnostic evaluation (see Table 707-1), including dual-energy x-ray absorptiometry. The use of bisphosphonates may be considered if the diagnostic evaluation does not reveal other underlying causes. The utility of early weight bearing has been advocated, but passive standing may have little impact on bone density. **Neurogenic bladder and bowel** can be anticipated (see Chapters 543 and 606.1). The goals of treatment interventions are to protect kidney function and achieve social continence. The introduction of clean intermittent catheterization is the mainstay of management. It is not atypical for newborn babies to be started on a clean intermittent catheterization program. Urodynamics and renal ultrasounds are routinely used to monitor for hydrenephrosis and track intravesicular pressures. Medications may be used to reduce bladder contractions and improve volume capacity. Surgical techniques are being used to improve continence, including bladder augmentation and the Mitrofanoff procedure (appendicovesicostomy). Symptomatic urinary tract infections should be treated with appropriate antibiotics. These children tend to have colonized bladders and should only be treated for symptoms and not the urinalysis or culture. A good bowel program is generally needed to achieve bowel continence. Nonsurgical interventions include adequate hydration, dietary manipulation, fiber regulation, and use of laxatives. Surgical interventions, such as the antegrade continence enema, have improved continence in many of these children and adolescents. **Latex allergies are fairly common in this population.** The etiology may be multifactorial but increased exposure may play a role in development of severe reactions (see Chapter 149). Care providers need to be keenly aware of products that contain latex or that have a cross reactivity such as foods mixed with avocado, bananas or Kiwi fruit. **Radioallergosorbent testing** is used for identification of potential severe allergens.

Spina bifida is known to be associated with specific **neuropsychologic problems**. Various cerebral neuronal dysplasias may be present. The hallmark is a nonverbal learning disorder characterized by difficulties in math reasoning, visual spatial perception, and time concepts. In addition there are weaknesses in executive function, processing speed, and organizational skills. Children with spina bifida typically fall within the average IQ range although those with a higher lesion tend to cluster on the lower range. Hydrocephalus itself has an impact on cognition as noted by deficits in learning, memory, and executive function. Young children with spina bifida tend to do well early on as they have good verbal skills but as the academic demands increase school problems become more obvious. It is important to have appropriate neuropsychologic/educational testing done to identify difficulties each child or adolescent may encounter. Appropriate early intervention and support programs should be put in place and **individual education plans** or 504 plans developed (see Chapter 36). Structure in the home environment plays a key role in teaching self-care, dressing, and mobility skills. The importance of these early interventions cannot be underestimated as they will impact the quality of life and independence in adolescence and transition to an independent adulthood.

### ADOLESCENCE AND TRANSITION INTO ADULTHOOD

Clinical care has increased the life span of individuals with spina bifida and the majority are living into adulthood. The physical problems in association with the learning disorders make the transition into independent living and competitive employment very difficult. The pediatrician in conjunction with specialty services plays a pivotal role in developing future planning. It is important to discuss early on strategies to encourage developmentally appropriate independence and self-help skills. Long-term financial arrangements, such as Special Needs Trusts, should be discussed. Transitioning primary and specialty care will need to be researched and introduced to the individual and family. Young adults may have depression and suicidal ideation.

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


Assistive devices, such as orthoses, prostheses, walkers, crutches, and wheelchairs, are key components of the therapeutic prescription for children with physical disabilities. The type of device chosen depends on the underlying diagnosis, functional level of the child, prognosis for improvement, tone abnormalities, range of motion, strength, and the overall gait pattern. Physicians, licensed independent practitioners, and physical therapists perform the evaluation of a child requiring mobility assistance. The physician or licensed independent practitioner is ultimately responsible for writing the prescription for the assistive device.

**ORTHOSSES**

An orthosis is a device that is applied to the surface of the body to maintain alignment or position, to prevent or assist movement of the body part, or to provide support. Orthoses can be static, indicating the brace is rigid and does not allow movement, or they can be dynamic,
allowing movement of the limb to occur. Orthoses are named for the body parts covered. For example, “AFO” stands for ankle-foot orthosis, a brace worn on the foot that extends from the toes to the midcalf position (Fig. 716-1). Orthoses are custom made by an orthotist and can be obtained either directly through the orthotist or through the child’s physical therapist. The orthosis is replaced during periods of growth or changes in function. All braces must be prescribed by a physician or licensed independent practitioner.

The type of lower-extremity orthosis prescribed is based on evaluation of the child’s gait, strength, tone, and range of motion. There are many types of braces that have specific functions to improve gait. Table 716-1 lists examples of these orthoses and their potential uses.

Solid and articulated AFOs are the most commonly prescribed braces. Solid AFOs are used for children with hypertonicity, as they help to biomechanically reduce tone and provide stability with standing. Solid-ankle AFOs are also used in children who are nonambulatory to maintain range of motion of the ankle.

Articulated (hinged) AFOs allow the child with active ankle dorsiflexion to achieve heel strike and a more typical-appearing gait pattern by allowing forward movement of the tibia. This design makes ambulating on uneven surfaces and using stairs easier because of the movement allowed at the ankle, while still supporting the foot position and medial-lateral stability of the ankle. Articulated AFOs should not be used in children with cerebral palsy, spina bifida, or other disorders if they have a crouched gait pattern because the braces do not prevent crouching and may, in fact, allow further crouching. With crouched gait the hips and knees are held in flexion and ankles in dorsiflexion throughout the gait cycle.

**PROSTHESSES**

A prosthesis is a device that replaces a missing body part, such as an arm or a leg. Lower-extremity prostheses are used to improve mobility, while upper-limb prostheses are not always needed to improve function as children can be quite independent with a single upper limb. Lower-limb prostheses are used in children with congenital amputations, limb deficiencies such as fibular longitudinal deficiency, and acquired amputations as a result of trauma or cancer.

There are multiple components to lower-limb prostheses, which include the socket and foot, but may also include a hip and knee joint depending on the level of amputation. A prosthetist works with the child and family to fabricate the prosthesis. A physician or licensed independent practitioner with experience in prostheses provides the prescription for this device.

The type of prosthesis and the age at which a child is fit for the device depends on the etiology of the amputation, healing after surgery, and weight-bearing restrictions. In very young children, use of a lower-extremity prosthesis follows developmental milestones, with the first prosthesis prescribed at the time the child is pulling to stand. Addition of joints to the prosthesis also occurs when developmentally appropriate, such as use of a knee joint around the age of 3 when the child is learning to use stairs.

Advances in technology are helping children who use prostheses achieve a fluid gait pattern that makes their prosthetic use virtually undetectable to the untrained eye. New components and designs allow amputees to lead active lifestyles, including running, swimming, biking, and mountain climbing.

**ASSISTIVE DEVICES**

The purpose of assistive devices is to provide a wider base of support to improve stability during ambulation. The least supportive device is a traditional single-point cane commonly used following an orthopedic injury. For most children with gait abnormalities secondary to neurologic disorders, this is not a functional option. More supportive gait aids, such as forearm or Lofstrand crutches, are appropriate in these children; however, use of these devices requires good coordination and strength. Children with cerebral palsy and spina bifida may benefit from these devices.

Walkers provide more support than crutches and canes; they do not require as much strength and coordination to operate. Children with cerebral palsy, for example, may use a reverse walker, which they pull behind them. This reverse configuration provides a wide base of support and stability, helps to maintain an erect posture, and allows the child to engage with the environment without the barrier of the walker in front of them. Having the walker behind them also reduces the risk for more serious injury after a forward fall.

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**Table 716-1 Orthotic Options**

<table>
<thead>
<tr>
<th>Orthosis</th>
<th>Function</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot orthosis</td>
<td>Provides support of foot only</td>
<td>Not typically customized</td>
</tr>
<tr>
<td>Supramalleolar orthosis</td>
<td>Provides medial-lateral support</td>
<td>Appropriate for children with low tone such as in Down syndrome</td>
</tr>
<tr>
<td>Ankle–foot orthosis</td>
<td>Provides support at the ankle and reduces footdrop or plantarflexion tone</td>
<td>Commonly used for ambulatory and nonambulatory children</td>
</tr>
<tr>
<td>Ground reaction ankle–foot orthosis</td>
<td>Provides knee extension moment to reduce crouching</td>
<td>Appropriate for children with spina bifida who crouch when walking</td>
</tr>
<tr>
<td>Knee–ankle–foot orthosis</td>
<td>Provides support at the knee when there is quadriceps weakness</td>
<td>Less commonly used because of large size of brace</td>
</tr>
</tbody>
</table>
For children who require a significant amount of support, gait trainers are often used. These devices allow the child to work on leg movements while the trunk and pelvis are stabilized (Fig. 716-2).

**WHEELCHAIRS**

Wheelchairs should be considered as a means of mobility when ambulation is not possible or is difficult outside of the home setting. Children with spinal cord injuries, spina bifida, neuromuscular diseases, or cerebral palsy may benefit from the use of a wheelchair. The goal is to provide a wheelchair that will allow the child to move independently about the environment, including home, school, and the community. Children as young as age 2 yr can self-propel a manual wheelchair and drive a power wheelchair. The type of wheelchair will depend on the child’s underlying diagnosis, cognitive abilities, vision, motor skills such as head and trunk control, ability to manually propel a wheelchair, strength and endurance, musculoskeletal deformities if present, and medical comorbidities. One must also consider future growth or anticipated changes in function over time as well as the family’s ability to transport the chair. Unique to pediatric wheelchairs is the adjustability to accommodate growth. A typical wheelchair may last 3-5 yr with periodic adjustments to growth by a seating specialist. There are many components that can be added in order to provide more support in the wheelchair, including head rests, lateral trunk support, hip guides, antitippers that prevent the wheelchair from tipping backwards, and specialized tires. The seating system is considered a separate item from the wheelchair itself and should be properly fit for the child’s current size and seating needs. Seats that are too large for the child can cause pressure ulcers, worsen scoliosis, and make it more difficult for the child to maneuver or propel.

*Bibliography is available at Expert Consult.*
Bibliography

See also Chapter 42.

The number of children with developmental disabilities in the United States has increased by 17% in the past 20 yr, with nearly 3 million being of school age. Despite available medical support, many of these children and their families do not receive recommended childhood preventive care and anticipatory guidance, health education, discussions about appropriate activity and exercise, or an opportunity to engage in or learn about health promotion.

The expansion of the disability definition to include children with special healthcare needs, chronic conditions, and activity limitations from any cause (e.g., limitations in usual daily activities such as age-appropriate self-care, mobility, communication, and cognition) has made the health issues of the more traditional childhood disability types (e.g., cerebral palsy, intellectual disability, spina bifida, congenital musculoskeletal disorders) more difficult to identify. U.S. data identify developmental, emotional, and behavioral conditions as the leading conditions with activity or functional limitations, with physical health conditions comprising a smaller proportion of self-identified disabilities (although mobility and motor control issues may be noted among the aforementioned nonphysical conditions). Childhood cognitive, mental, and physical health problems contribute to continued economic and health problems into adulthood. Because these problems can respond to childhood and adolescent health promotion interventions, monitoring children with disabilities throughout their development is helpful in providing information and support to children and adolescents, their parents, and families to promote health over a lifetime.

HEALTH PROMOTION DEFINITIONS AND BACKGROUND FOR DISABILITY

The World Health Organization defines health promotion as “the process of enabling people to increase control over, and to improve, their health.” For people with disabilities, this concept is important because they are both underserved and have comparatively large health disparities. The World Health Organization further defines health promotion approaches as including more than health education, and consisting of community action, supportive and accessible environments, policy changes, health service modifications, and development of personal skills. Health and wellness programs also include traditional preventive management strategies, such as anticipatory guidance. There is ample evidence that engaging in specific areas of health promotion results in improvement, although the evidence for its influence on adult health is less robust.

Children with disabilities encounter many barriers to healthy behaviors (Table 717-1). Both broad and focused health promotion programs consider severity of condition, barriers and resources, and self-efficacy and resiliency, to achieve health-promoting behaviors. Children with disabilities may also require modeling or assistance to apply healthy behaviors to their particular disability or economic, social, and environmental circumstances.

Children and adults (and their families) often view health differently than those without disabilities. Disability may influence health and vice versa, but their perception of their own health and wellness does not equate with their level of disability. Children with congenital or
acquired disabilities have a narrow view of healthy living, concentrating on nutrition and secondarily on physical activity, with little understanding of how they apply to their own condition. Experiences as a child with a disability often foreshadow adult behaviors, especially negative attitudes toward therapy, exercise, and activity. Beliefs of parents, families, and healthcare providers also influence the views of health by children with disabilities. Health promotion programs for these children must (1) understand and support the role and well-being of parents, (2) recognize that parents of children with more functional limitations may require more resources and support, (3) involve children with disabilities in design of programs and decisions about participation, and (4) address barriers to participation, perceived and real (see Table 717-1). Because many healthcare providers have a poor understanding of the needs of people with disabilities, engaging experienced rehabilitation health professionals in designing and promoting a health and wellness agenda is an important strategy.

An effective health and wellness program should involve multiple approaches and opportunities for success, including partnerships with families, school staff, and rehabilitation providers. Competency requires addressing any mismatch between the child’s positive sense of health and well-being and that expected by the healthcare providers; limitations of an education-only model; engaging the child in discussions about the importance of healthy behaviors, ways to engage in healthy behaviors related to the child’s disability and circumstances, and decisions about participation; and parent and family involvement coupled with sensitivity for the already overwhelming support a family provides for the child with a disability.

**ANTICIPATORY GUIDANCE, COUNSELING, AND PREVENTIVE CARE**

Preventive healthcare through health education, anticipatory guidance, and participation in screening and immunization schedules is the mainstay of pediatric public health programs (see Chapter 16). *Bright Futures*, developed by the American Academy of Pediatrics and their collaborators and supported by the Maternal and Child Health Bureau, Health Resources and Services Administration, provides a knowledge base for pediatric healthcare providers and the public about anticipatory guidance, health promotion, and prevention for children and adolescents; but it has few references to disability. Anticipatory guidance refers to general information related to growth/development and healthy practices. Counseling refers to advice given regarding specific conditions, which could include discussions of applications of general guidance to children with disabilities. For the general population, 25% of parents receive no information and <50% receive all recommended guidance. Although parents of children with special healthcare needs (the broad inclusive definition of disabilities) report similar or better receipt of general preventive information, it is not clear whether those with higher severity of functional limitations receive this guidance or counseling, and whether it is provided in the context of disability and other circumstances.

Children with special healthcare needs require typical prevention, as well as more specific counseling related to their disability. Some of this more specific counseling can be managed by specialty care providers, although children with special healthcare needs have difficulty obtaining appropriate specialty outpatient services. Additional barriers to care, especially with increasing age of the child, are the lack of accessible medical equipment and facilities. Although discussions of health with adolescents about smoking, drinking, and protected sexual activity should be undertaken, the discussions may require a different focus for adolescents with disabilities. Higher violence and abuse rates toward children with disabilities are reported for which providers must be vigilant.

The recommendation is to recognize the need for modifications to typical guidance, to be alert for any signs of violence, and to broaden counseling to include questions and discussions about conditions associated with the specific disabilities (e.g., epilepsy or cognitive impairments often seen with cerebral palsy, or neurogenic bladder and bowel in spinal cord dysfunction) or secondary conditions, such as pain, osteoporosis/fractures, or fatigue seen in many children and adolescents with disabilities. Although the patient-centered medical home may provide this inclusive support, it risks decreased access to the specialty physicians and healthcare providers who will provide much of this information.

**PHYSICAL ACTIVITY AND EXERCISE**

National health guidelines recommend at least 60 min of physical activity daily for children, and they suggest that specific advice from health professionals is needed for children with disabilities. Exercise and activity have shown to increase aerobic capacity, functional ability, and quality of life for children with many kinds of disabilities and chronic diseases (e.g., cerebral palsy, spinal cord dysfunction, cystic fibrosis, asthma, intellectual disabilities, diabetes). The vast majority of study participants noted benefits. And yet, most healthcare providers expect sedentary lifestyles for children and adolescents with disabilities, whatever their functional abilities. For children with disabilities, school physical education and recess programs can support activities at or greater than the recommendation, and school requirements can reinforce activity expectations. Despite this potential, most children with disabilities engage in very limited physical activity even in supported school environments. School and public playgrounds are not sufficiently accessible to support community physical activity.

Physical activity for children and adolescents improves fitness and quality of life for youth with developmental disabilities (Table 717-2). The described exercise and fitness programs require 2-3 mo of participation at least twice a week to achieve any changes, and many of the changes achieved are longer lasting than expected. These programs are not traditional therapy, and participation in therapy is not a substitute. The focused fitness and exercise programs cited here generally required the support and direction of rehabilitation professionals, although programs can be community based in nonmedical surroundings.
### Table 717-2 Examples of Effective Exercise Programs for Children with Disabilities

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>DESCRIPTION</th>
<th>OUTCOMES/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center-based fitness program and home program</strong></td>
<td>Children with a variety of disabilities Group exercise: 2x/wk for 14 wk; warm-up, aerobicics, strengthening, cool down Home program: 2x/wk for 12 wk using video exercises</td>
<td>Improved walking efficiency, strength, general function Group treatment more effective by measures and by satisfaction</td>
</tr>
<tr>
<td><strong>Group aquatics aerobic exercise program</strong></td>
<td>Children with a variety of disabilities, &gt;50% able to walk 2x/wk for 14 wk Recreation to achieve target heart rate; aquatic strengthening program</td>
<td>Improved walk/run, not strength to isometric testing Required adults monitoring to maintain target heart rates</td>
</tr>
<tr>
<td><strong>Group training class</strong></td>
<td>Children with cerebral palsy able to walk 2x/wk for 4 wk Warm-up, circuit training stations (treadmill, balance, stairs, closed-chain exercises)</td>
<td>Improved muscle strength, mobility, function except fine-motor test–maintained 8 wk later Therapists conducted and monitored</td>
</tr>
<tr>
<td><strong>Strength training</strong></td>
<td>Children with cerebral palsy, including a majority able to walk with assistive devices 3x/wk for 6 wk Progressive strengthening program, conducted in the home</td>
<td>Improved perceptions of strength, walking, stair management and improved psychologic benefits Clinicians to monitor, problem solve; some need for direct parental involvement</td>
</tr>
<tr>
<td><strong>Walking–jogging program</strong></td>
<td>Children with Down syndrome 3x/wk for 10 wk 30 min sessions, achieving 65-70% peak heart rate</td>
<td>Difficulty promoting increasing activity intensity Improved peak exercise time and grade, but not in aerobic capacity, improved walking capacity</td>
</tr>
<tr>
<td><strong>Treadmill training program</strong></td>
<td>Children with intellectual disabilities Daily for 2 mo Progressive treadmill use with goal of 20-30 min</td>
<td>Improved heart rate with and without activities Therapist developed and monitored, community staff implemented</td>
</tr>
<tr>
<td><strong>Peer-guided exercise</strong></td>
<td>Adolescents with intellectual disabilities 2x/wk for 15 wk Typical adolescents and those with disabilities paired to support each other in 1 hr aerobic, weight-training, flexibility activities</td>
<td>Improved curl-ups, 6 min walk, and body mass index High attendance, less compliance with weight training</td>
</tr>
</tbody>
</table>

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Recreation and organized sports are other areas where children and adolescents with disabilities can engage successfully, at times with modifications. Participation has many biophysical, psychological, and social benefits. Programs through Special Olympics International are an opportunity for children and adolescents to engage in supportive and monitored environments for sport and recreation.

### NUTRITION AND OBESITY

Managing the combination of nutrition and physical activity is the key ingredient of weight control. Obesity is a significant problem affecting a large portion of the general population, including children with special needs. Estimates suggest that children with physical activity limitations were twice as likely as the general population to be overweight and youth with cognitive impairments are at increased risk. It is unclear if obesity is a cause for the activity limitations or is a result of the limited activity, which may be an important distinction in developing interventions. The concern with obesity contrasts with early life weight gain needs of many children with disabilities, and may pose important management confusion for parents and families with the change of focus to weight decrease. Confounding factors include (1) the propensity of some disabilities, usually those that are genetically mediated, to be associated with obesity; (2) standards of measurement may not be appropriate for certain diagnoses or disability types (e.g., expected body composition differences, short stature, contractures, or limb deficiencies or amputations); (3) obesity may be a side effect of medication and must be weighed against benefits (e.g., antidepressants, mood stabilizers, steroids); and (4) the social network of family, friends, schools, and healthcare providers may unwittingly influence healthy habits in a negative way, including use of food as reward for behavior management.

### EMOTIONAL HEALTH AND LEISURE ACTIVITIES

Emotional health is often overlooked in children with disabilities, unless mental health or challenging behaviors are the cause for the disability. Youth and adolescents with disabilities appear to be at higher risk for feeling low, stressed, or anxious (especially those with higher levels of limitations), and those with mental health needs may have lower adaptive functioning, a family history of mental illness, or a diagnosis of autism spectrum disorder. Adolescents with physical disabilities participate in fewer social activities, have fewer close or intimate friends, and have few plans for ongoing education. There is a risk for continued isolation into adulthood. Medications may be considered, but effectiveness is not guaranteed and unwanted side effects may produce more health conditions. Counseling requires insurance support or discretionary funding.

Leisure and recreational activities provide social supports, additional stress-coping mechanisms, and ability to develop social skills and a stronger personal identity. Girls with disabilities tend to engage...
in social or skill-based activities, and boys in physical activities, with decreasing participation with increasing age. Rehabilitation professionals can assist with problem-solving activities, such as using computerized technologies (e.g., Wii, Xbox), adaptation of equipment (e.g., modified upper-limb prosthesis to allow baseball glove use), and knowledge of adapted recreation programs in the area (e.g., horseback riding, winter/water sports) to increase participation.

**DENTAL CARE**
Dental care is a frequently unmet health care need for children with disabilities. The principal deficits are in receipt of further or specific dental care (not preventive services) and that condition severity and low income may be associated with unmet dental needs. Challenging behaviors often limit dental care, and the use of behavior management techniques and education programs have been effective in allowing both preventive and additional dental care.

**ROLE OF HEALTHCARE PROVIDERS**
Healthcare providers should have higher expectations for health and healthy behaviors for children with disabilities. Healthy behaviors do not come naturally to most people, including children with disabilities and their families, and there is a role for healthcare providers in providing a better understanding of health and behavior change concepts. Primary care and other healthcare providers should be mindful of discussing and promoting healthy behaviors with children and adolescents with disabilities and their families (Table 717-3).

*Bibliography is available at Expert Consult.*
Bibliography


BASIC PRINCIPLES
Radiation exposure occurs from both natural (50%) and manmade (50%) sources. Radon gas accounts for the majority (37%) of natural radiation. The contribution of medical radiation has dramatically increased to 50% in 2006 from 15% in the mid-1980s. CT is responsible for 24% of all radiation exposure and almost half of manmade radiation (Fig. 718-1). Medical radiation is concerning. Estimates of dose risks ranging from no risk to as much as 2% of all cancers in the United States may be attributable to radiation from CT studies. Studies implicate CT examinations in childhood with subsequent development of cancer. In addition, radiation doses from medical imaging can be poorly understood. Seventy-five percent of radiologists and emergency department physicians are reported to underestimate the radiation dose from CT. Some imaging procedures do not produce radiation (Table 718-1), and not all radiation-producing modalities expose a child to the same amount of radiation (Table 718-2).

Nuclear medicine and positron emission tomography examinations are described by the amount of radioactivity injected (millicuries or becquerels) or are converted to effective dose (milliSieverts). The units of absorbed dose, as defined by the International Commission of Radiation Units, are the rad, introduced in the 1960s, and the Gray (Gy), introduced in 1985. The metric used in denoting biologic response is the rem (older unit) and the Sievert (Sv) (Table 718-3). Equivalent dose and effective dose are measured in Sv and mSv. Not all radiation has the rem (older unit) and the Sievert (Sv) (Table 718-3). Equivalent dose is introduced in 1985. The metric used in denoting biologic response is the rem (older unit) and the Sievert (Sv) (Table 718-3). Equivalent dose and effective dose are measured in Sv and mSv. Not all radiation has

BILOGIC EFFECTS OF RADIATION

Biologic effects of radiation are divided into 2 types. Tissue reactions (previously deterministic effects) (determined by the dose) are characterized by a threshold dose and severity is directly related to the magnitude once the threshold is exceeded. For example, cataracts have traditionally been reported to occur with an acute exposure to >2.0 Gy or with long-term exposure to >5.0 Gy (Table 718-4), although publications indicate lower thresholds as well as debate about these thresholds. Tissue reactions never occur from the radiation organ doses generally used in single diagnostic examinations (<100 mGy), but invasive procedures (therapeutic and interventional) have on rare occasions led to these effects. Stochastic (random) effects are of concern because they can occur at any dose; that is, there is no threshold, with the probability of an effect increasing with rising dose. These effects can be caused by any radiation striking vulnerable tissue (most importantly DNA, but cytoplasm also may be at risk) and causing irreversible damage. These effects lead to the linear no (dose) threshold model, which states that radiation damage increases with rising dose in a linear fashion. This concept stresses that no level of radiation exposure can be considered to be absolutely safe.

Radiation can cause permanent cell injury, carcinogenesis, genetic mutations, or cell death. The biologic effects of radiation result primarily from damage to DNA directly (direct effect) through interaction of fast recoil electrons caused by the absorption of x-rays (one third of the damage) or secondarily by the formation of free radicals (indirect effect). Approximately 80% of the cell is water, so most of the energy deposited in a cell results in production of aqueous free radicals. The reactions are rapid (10^-18 to 10^-3 sec). A dose of 10 mGy results in approximately 10^18 ionizations per cell type. The biochemical and physiologic changes that follow take hours or days, whereas the induction of cancer may take a few years to decades.

The manifestations of DNA injury are variable. The cell containing the damaged DNA might die; cell death (apoptosis) is a mechanism for eliminating heavily damaged and potentially mutable cells. Damage to a base pair is the most prevalent and least significant effect. Breaks of a single strand of DNA usually have little biologic significance because each strand is repaired with use of the opposite strand as a template, but a mutation can result if misrepair occurs.

Breakage of both strands of DNA (the least-common event) is more problematic. The end result seems to depend on the proximity of the break in each strand. If widely separated, repairs occur as with a single-strand break. If the breaks in the 2 strands are opposite each other (or separated by only a few base pairs) repair is more difficult without a template. This type of break is the mechanism of radiation-induced cell death, chromosomal damage leading to mutations, and carcinogenesis.

When DNA damage occurs, aberrations are produced in chromosomes, resulting in an unstable aberration (usually lethal to dividing cells) or stable aberration. Stable aberrations can result in failure of chromosomes to recombine (leading to deletions) or in abnormal rearrangement of chromosomes, such as reciprocal translocation or aneuploidy. Although it is logical to think that these abnormalities in chromosomes lead to mutations that can activate oncogenes or protooncogenes or cause mutations in tumor-suppressor genes (see Chapter 492), few radiation-induced cancers show specific translocations such as would be associated with activation of specific oncogenes or known tumor-suppressor genes. An exception is the radiation induction of papillary thyroid carcinoma in children, which probably results from activation of the RET oncogene (see Chapter 506).

Radiation carcinogenesis seems to be a progressive multistep process composed of 3 independent stages: morphologic changes, cellular immortality, and tumorigenicity. Radiation exposure induces cellular genomic instability. This instability is transmitted to a cell's progeny, resulting in a continued elevation in the rate at which genetic changes arise in the subsequent generations of the irradiated cell (Fig. 718-2).

A longitudinal study of the lifetime risks of excess cancer mortality secondary to irradiation has been evaluated in atomic bomb survivors. More than 86,000 survivors have been followed for more than 65 yr since exposure. Individual radiation doses were estimated by considering the person's location in relation to distance from the epicenter and individual shielding situations. Most of the exposure was direct gamma irradiation, with some neutron exposure. Age at exposure and ethnic differences in cancer occurrence influence the sensitivity to radiation-induced cancers (Fig. 718-3). Compared with the middle-aged adult, children are 2-10 times more sensitive to radiation-induced carcinogenesis, and the youngest neonate is more sensitive than the older child. Because of the higher risks associated with breast and thyroid cancer, girls are more sensitive than boys. It must be understood that
cancer rates in this study are mortality figures. The incidence of cancer in this population is approximately 2 times greater than mortality incidence.

The doses used in diagnostic radiology for multidetector CT scans overlap with low-dose induced cancer in atomic bomb survivors (Fig. 718-4). Estimates for lifetime risk of cancer following head and abdominal CT scans in children vary widely, from as low as 1:500 to more than 1:10,000 (including the possibility that these doses do not incur a risk). Therefore, since stochastic effects are random but increase with rising dose, it is mandatory that we use the lowest dose necessary to get sufficiently diagnostic images. The advent of digital picture archiving communication systems utilizes postprocessing algorithms and can make all images diagnostic, even those with higher-than-necessary exposures. Since the elimination of film-based systems, where overexposures were evident as “dark” films, digital technology eliminates the imager’s ability to know whether enough or too much radiation was given. It does not allow the imager to determine whether the patient received “as low as reasonably achievable” radiation dosing. It is for this reason that some radiation metric (and familiarity with this metric) should appear on each image.

Increased biologic vulnerability to radiation can be seen in the fetus exposed in utero through maternal radiation. In utero radiation exposure is associated with a 92% excess risk of dying from leukemia.

**Table 718-2**  Radiation Dose by Imaging Test

<table>
<thead>
<tr>
<th>EXAMINATION</th>
<th>DOSE</th>
<th>SITE MEASURED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest—2 views</td>
<td>0.1-0.2 mGy</td>
<td>Entrance (skin)</td>
</tr>
<tr>
<td>Abdominal—2 views</td>
<td>0.5-1.0 mGy</td>
<td>Entrance (skin)</td>
</tr>
<tr>
<td>Fluoroscopy Nonpulsed</td>
<td>3-5 mGy/min</td>
<td>Entrance (skin)</td>
</tr>
<tr>
<td>Pulsed</td>
<td>1-3 mGy/min</td>
<td></td>
</tr>
<tr>
<td>Computed tomography(^1)</td>
<td>Head (2 yr old)</td>
<td>20-30 mGy</td>
</tr>
<tr>
<td>Abdomen (2 yr old)</td>
<td>2-3 mGy</td>
<td>Midiameter of phantom of 32 cm</td>
</tr>
<tr>
<td>Nuclear medicine(^1)</td>
<td>(technetium (^{99m})Tc mercaptoacetyltriglycine—renal)</td>
<td>120 mSv</td>
</tr>
<tr>
<td>Positron emission tomography(^1)</td>
<td>(brain fludeoxyglucose (^{18})F)</td>
<td>185 mSv</td>
</tr>
</tbody>
</table>

*Background radiation = 0.01 mSv/day or 3 mSv/yr.

\(^1\)Scan explained as CT dose index (CTDI). First dose is with adult factors; second dose, shown in parentheses, is examination adjusted for children.

**Table 718-4** Deterministic Dose Rates

<table>
<thead>
<tr>
<th>INJURY</th>
<th>APPROXIMATE THRESHOLD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
</tr>
<tr>
<td>Transient erythema</td>
<td>200 rad (2 Gy)</td>
</tr>
<tr>
<td>Dry desquamation</td>
<td>1,000 rad (10 Gy)</td>
</tr>
<tr>
<td>Moist desquamation</td>
<td>1,500 rad (15 Gy)</td>
</tr>
<tr>
<td>Temporary epilation</td>
<td>200 rad (2 Gy)</td>
</tr>
<tr>
<td>Permanent epilation</td>
<td>700 rad (7 Gy)</td>
</tr>
<tr>
<td><strong>EYES</strong></td>
<td></td>
</tr>
<tr>
<td>Cataracts (acute)</td>
<td>&gt;200 rad (2.0 Gy)*</td>
</tr>
</tbody>
</table>

*Has been reported as occurring between 0.5 and 1.0 Gy.

Modified from Hall EJ: Radiobiology for the radiologist, ed 5, Philadelphia, 2000, Lippincott Williams & Wilkins.

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**Figure 718-2** Schematic of radiation-induced mutagenesis. Open circles represent normal wild-type cells, whereas solid blue circles represent mutated cells. A, Most of the cells in an irradiated population retain the wild-type phenotype. B, Example of a cell directly mutated by radiation exposure; the mutation is transmitted to all of its progeny. C and D are examples of mutations arising as a result of radiation-induced genomic instability. The irradiated cell and its immediate progeny are wild type, but the frequency with which mutations arise among the more distant descendants of the irradiated cell is elevated. (From Little JB: Ionizing radiation. In Kufe DW, Pollock RE, Weichselbaum RR, et al, editors: Holland-Frei cancer medicine, ed 3, Ontario, Canada, 2003, BC Decker.)

**Figure 718-3** Lifetime risk of excess cancer per Sievert (Sv) as a function of age at the time of exposure. Data from the atomic bomb survivors. The average risk across all ages in a population is approximately 5% per Sievert, but the risk varies considerably with age: children are much more sensitive than adults. At early ages, girls are more sensitive than boys. (From Hall EJ: Introduction to session I: Helical CT and cancer risk, Pediatr Radiol 32:225–227, 2002.)

**Figure 718-4** Relevant dose range for pediatric CT: 6-100 mSv (0.006-0.1 Sv). There is direct, statistically significant evidence for risk in the dose range from 0-0.1 Sv. (From Brenner DJ: Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative, Pediatr Radiol 32:228–231, 2002.)

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before age 10 yr and a 180% excess risk of dying from other malignant diseases. Even 40 yr later there is a 228% increased relative risk of cancer associated with radiation in utero.

The fetus and infant are most vulnerable to radiation-induced cancer because (1) they are growing rapidly, with many cells undergoing mitotic activity; (2) radiation-induced tumors (except leukemia) take a long time to develop and children have a longer lifetime; and (3) there is a greater time to have imaging studies, with accumulation of the risks related to doses.

Most childhood tumors occur sporadically, but 10-15% of cases have a strong familial association. Familial tumors have specific chromosomal deletions in common. In some of these tumors (retinoblastoma), the 2-hit hypothesis by Knudson is apparent (see Chapter 491). It is not coincidental that individuals with many of the congenital diseases are at risk for the development of tumors after irradiation.
Late Effects of Radiation Therapy in Inherited Human Syndromes Associated with Sensitivities to X-Rays

<table>
<thead>
<tr>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Basal cell nevoid syndrome</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
</tr>
<tr>
<td>Down syndrome</td>
</tr>
<tr>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Gardner syndrome</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
</tr>
<tr>
<td>Usher syndrome</td>
</tr>
</tbody>
</table>


Table 718-5 lists diseases that are associated with sensitivity to radiation.

DECREASING UNNECESSARY DIAGNOSTIC RADIATION IN CHILDREN WHILE STILL OBTAINING DIAGNOSTIC IMAGES

Selecting the correct examination is the responsibility of the ordering physician and may involve consultation with the radiologist, preferably with pediatric expertise. Evidence-based medicine has shown little yield from an imaging work-up (including CT) of a child with a single nonfebrile seizure without other neurologic abnormalities. This is especially true if there is no antecedent history of abnormal behavior or of personality or developmental change. CT does not detect as many abnormalities as MRI, and CT involves ionizing radiation. MRI detects the subtle changes of congenital or acquired anomalies that may be responsible for seizures much more easily. Therefore, it is appropriate, except in an emergency situation, to obtain MRI within a reasonable time frame instead of performing 2 tests (CT followed by an MRI).

Reducing Radiation from the CT Examination

The most common source of medical radiation is CT. We have progressed from a single-slice scanner to scanners that can obtain up to 320 slices in a second. The images have excellent detail, including multiplanar and 3-dimensional reconstruction of the acquired data. It once took more than 30 min to obtain 10-12 images, but now hundreds to thousands of images are generated in seconds. When adult parameters for CT settings are used for children, the dosage for children is actually higher than the dosage for adults. This occurs because lower-energy x-rays that would have been absorbed in the near field in an adult pass into the entire child, irradiating all organs. When comparing dosages given to newborns and adults during CT scanning of the head, with the same parameters in both groups, the dosage given to newborns is 4 times that of the dosage given to adults. With abdominal imaging, the dosage is increased by 60%.

It is the role of the radiologist to tailor the examination to the pediatric patient. One can determine whether the examination is tailored to the pediatric patient by looking at the dose report or the parameters of tube current (milliamperage/second [mAs]) and peak kilovoltage (kVp). Scanning range should be limited to only the necessary area. Multiphase scanning should only be obtained when necessary. The radiologist has many ways to decrease parameters so that children receive diagnostic imaging without excessive radiation. In some instances, reducing the radiation dose by half, even in adults receiving CT, does not change the diagnostic efficacy of the study and the radiologist’s ability to make the proper diagnosis.

RADIATION THERAPY—ACUTE AND LATE EFFECTS

Radiation therapy uses high doses to kill malignant cells. The sensitivity of normal cells is quite close to that of malignant cells, and to achieve significant cure rates, radiation oncologists must accept a given percentage of serious complications (5-10%). Radiation causes tissue loss plus injury to the underlying vasculature. The vascular change may be progressive, leading to arteriocapillary fibrosis and irreparable injury, in turn leading to further tissue loss.

The acute effects of therapy (occurring less than 3 mo after therapy begins) are usually related to the area of the body being irradiated (except fatigue, which can begin during this time period). These acute effects include radiation-caused pneumonitis, dermatitis, mucositis and esophagitis, cerebral edema, and swelling of the organ irradiated. There may be changes in bowel movement patterns. Of these, one of the most severe acute reactions is pneumonitis. It can be manifest within 24 hr of irradiation when there is an exudation of proteinaceous material into the alveoli and intraalveolar edema. Most often, however, radiation pneumonitis begins 2-6 mo after the beginning of radiation with a clinical presentation of fever, cough, congestion, and pruritic pain. The late effects of therapy (beginning more than 3 mo after therapy) are numerous (Table 718-6). The most common are abnormalities of pulmonary function, hearing loss, endocrine/reproductive function, cardiac function, and neurocognitive loss.

Annually, childhood cancer affects 70-160 per million children between the ages of 0 and 14 yr. Because of earlier diagnosis and improved therapy, more than 79% of children who were diagnosed from 1995-2001 with cancer are long-term survivors. Approximately 1 in 570 young adults is a long-term survivor of cancer, and up to 25% have a complication related to their therapy. Second cancers account for 6-10% of all cancers in children or adults. Among children in the Childhood Cancer Survivor Study, there is a cumulative incidence of second neoplasms of 3.2% at 20 yr from original diagnosis. Primary malignancies with the highest cumulative incidence of a second neoplasm in the order of frequency are Hodgkin disease (7.6), soft tissue

Table 718-6

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>LATE EFFECT</th>
<th>DOSE (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Muscular hypoplasia</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Scoliosis, kyphosis, lordosis</td>
<td></td>
<td>10-20</td>
</tr>
<tr>
<td>Osteocartilaginous exostosis</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Neuroendocrine (craniocerebral)</td>
<td>Impaired growth hormone</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone deficiency</td>
<td></td>
<td>&gt;40</td>
</tr>
<tr>
<td>Thyrotropin-releasing deficiency</td>
<td></td>
<td>&gt;40</td>
</tr>
<tr>
<td>Precocious puberty (females mostly)</td>
<td></td>
<td>&gt;20</td>
</tr>
<tr>
<td>Gonadotropin deficiency</td>
<td></td>
<td>&lt;40</td>
</tr>
<tr>
<td>Gonadal failure</td>
<td>Ovarian failure</td>
<td>4-12</td>
</tr>
<tr>
<td>Testicular failure</td>
<td></td>
<td>&gt;3</td>
</tr>
<tr>
<td>Central nervous system dysfunction</td>
<td>Structured changes</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Cognitive changes</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Other</td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ear impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone marrow dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac impairment</td>
<td></td>
</tr>
</tbody>
</table>

*With intrathecal chemotherapy (methotrexate).
sarcoma (4.0), cancers of bone (3.3), leukemia (2.1), central nervous system (CNS) cancers (2.1), and non-Hodgkin disease lymphoma (1.9). This reflects an overall standard incidence rate of 6.38% (Fig. 718-5). The most prevalent second tumors are bone, breast, thyroid, CNS, leukemia, sarcoma, melanoma, lymphoma, and other. Table 718-7 relates second cancers to primary cancer and latency period. Almost 70% of the second neoplasms are in the field of the original irradiation. Radiation therapy increases the risk of second cancers in a dose-dependent manner for nongenetic neoplasms.

The exact complications depend on the location of the treatment field. In children, because of the location of many childhood tumors, the normal brain is commonly in the treatment field. Standard irradiation of the brain in children results in cortical atrophy in more than half of patients who receive 2,000–6,000 rads; 26% are left with white matter changes (leukoencephalopathy) and 8% with calcifications. The younger the child is at the time of irradiation, the greater is the atrophy. Some patients also demonstrate mineralizing microangiopathy. Radiation-induced changes of the brain are potentiated by methotrexate administered before, during, or after radiation therapy.

Cerebral necrosis is a serious complication of radiation-induced vascular disease. It usually is diagnosed 1–5 yr after irradiation but can occur up to a decade later. Brain necrosis may manifest as headache, increased intracranial pressure, seizures, sensory deficits, and psychotic changes.

Spinal cord irradiation may result in radiation myelitis, which may be either transient or permanent. Acute transient myelitis often appears 2–4 mo after irradiation. Patients with myelitis usually present with Lhermitte sign, a sensation of little electrical shocks in the arms and legs occurring with neck flexion or other movements that stretch the spinal cord. Reversal of transient myelopathy usually occurs between 8 and 40 wk and does not necessarily progress to delayed necrosis. Delayed myelopathy occurs after a mean latent period of 20 mo but can occur earlier if the total dose or the dose per fraction is high. It usually manifests as discontinuous deterioration and is irreversible. In the cervical and thoracic regions, sensory dissociation develops, followed by spastic and then flaccid paresis. In the lumbar cord, flaccid paresis is dominant. The mortality for high thoracic and cervical lesions reaches 70%, death being due to pneumonia and urinary tract infections.

Central nervous system irradiation may also affect growth by compromising function of the pituitary-hypothalamic axis and leading to diminishing growth hormone production and release. Non–growth hormone trophins may also be affected by CNS irradiation, leading to gonadotrophin deficiency or precocious puberty. Central hypothyroidism can also develop. CNS irradiation also compromises bone mineral deposition both locally (in the radiation field) and systemically.

Irradiation also has other effects specific to children (see Table 718-6). Scoliosis and hypoplasia of bones may occur if fractionated treatment schemes exceed 4,000 rad. Fractionated doses higher than 2,500 rad can result in slipped capital femoral epiphyses. An increase in the incidence of benign osteochondromas also has been reported after childhood irradiation. Chest wall irradiation of girls (besides causing breast cancer) may impair breast development and/or cause fibrosis and atrophy of breast tissue.

WHOLE-BODY IRRADIATION

Uncontrolled Large- or Small-Scale Exposure to Radiation

Large-scale exposure to radiation can occur in an event of nuclear accidents, war, or terrorist attacks (see Chapters 39.2 and 723). Radiation as well as explosive and thermal injury need to be considered.
Clinical Manifestations

Table 718-8 presents dose–effect relationships for acute whole-body penetrating radiation. A large single exposure of penetrating radiation can result in acute radiation syndrome. The signs and symptoms of this syndrome result from damage to major organ systems that have different levels of radiation sensitivity, modulated by the rate at which the radiation exposure occurred. Delivery of 100 rads in 1 min would be symptomatic, but delivery of 1 rad/day for 100 days would not be symptomatic.

The hematopoietic syndrome results from acute whole-body doses above 200 rad. A prodromal phase consists of nausea and vomiting within the 1st 12 hr, with symptoms usually lasting up to 48 hr. A latent period of 2–3 wk, during which patients may feel quite well, follows. Although patients are asymptomatic, bone marrow impairment has occurred. The most obvious laboratory finding is lymphocyte depression (Table 718-9). Maximal bone marrow depression occurs approxi-
site for accidental localized irradiation injuries, usually as a result of picking up or playing with lost radiation sources. The second most common accidental site is the thigh and buttocks, predominantly from placing unsuspected highly radioactive sources in the pockets. Table 718-10 lists the skin changes that occur after a single acute, localized irradiation. As opposed to other forms of thermal burns, signs of irradiation appear a period of days after the exposure. Vascular insufficiency may appear months to years later and cause ulcerations or necrosis in formerly heated areas. The penetrability of the radiation is an important factor in the outcome of local radiation injury. Beta rays from heavy radiation fallout can cause superficial skin burns because they have low penetrability.

Some tissues that may receive localized radiation exposure are relatively radiosensitive. Cataract formation (see Chapter 628) may occur with single gamma ray exposures in the range of less than 1 Gv to several Gv. Such cataracts usually take from 2 mo to several years to develop. Oligospermia may take up to 2 mo to develop. Transient infertility in men may result from doses as low as 15 rad, and permanent sterility may occur in men at dose levels between 300 and 600 rad.

**Treatment**

Skin therapy is directed at prevention of infections. Treatment of localized injuries usually involves plastic surgery and grafting, if the radiation exposure was not very penetrating (see Chapter 75). The nature of the surgery depends on the dose at various depths in tissue and the location of the lesion. The full expression of radiation injury often is not apparent for 1-2 yr, owing to slow arteriolar narrowing that can cause delayed necrosis. After relatively penetrating radiation, amputation may be necessary because of oblitative changes in small vessels.

**INTERNAL CONTAMINATION**

**Epidemiology**

Accidents involving internal contamination are rare and are usually the result of misadministration in hospital settings or voluntary ingestion of unsuspected contaminated radioactive materials. Other possible causes of internal contamination of children include ingestion of breast milk from mothers who have had diagnostic nuclear medicine scans and radiation exposure when a parent or sibling receives a therapeutic dose of iodine-131.

**Clinical Manifestations**

The hazards from internal contamination depend on the nature of both the radionuclide (particularly in terms of its solubility in water, half-life, and radioactive emission) and the chemical compound.

**Treatment**

The most effective treatment requires knowledge of both the radionuclide and the chemical form. Treatment must be instituted quickly to be effective (Table 718-11). Removal treatment involves cleaning a contaminated wound and performing stomach lavage or administration of cathartics in the case of ingestion. Administration of alginate-containing antacids (e.g., Gaviscon) also usually helps in removal by decreasing absorption in the gastrointestinal tract. An example of blocking therapy is the administration of potassium iodine or other stable iodine-containing compounds to patients with known internal contamination with radioactive iodine. The stable iodine effectively blocks the thyroid, although its effectiveness decreases rapidly as time elapses after the contamination. The recommended dose of potassium iodine is 16 mg for neonates; 32 mg for children ages 3 yr or younger; and 65 mg for children ages 3-18 yr. Each dose protects for only 1 day. Dilution therapy is used in cases of tritium (radioactive hydrogen as water) contamination. Forcing fluids promotes excretion. Cases of internal contamination with transuranic elements (americium and plutonium) may require chelation therapy with calcium diethylenetriamine pentaacetic acid.

**EXTERNAL CONTAMINATION**

The presence of external radioactive contamination on a patient’s skin is not an immediate medical emergency. Management involves removing and controlling the spread of radioactive materials. If a patient has suspected surface contamination and no physical injuries, decontamination can be performed relatively easily. If substantial physical trauma or other life-threatening injuries are combined with external contamination, surface decontamination should proceed only after the patient has been stabilized physiologically. In many accident situations, essential medical care is delayed inappropriately by hospital emergency staff because of fear of radiation or spread of contamination in the hospital. After a radiation accident, triaging of patients is critical and is based on exposure and symptoms (Fig. 718-7).

**Table 718-10**

<table>
<thead>
<tr>
<th>ABSORBED DOSE (Gy)</th>
<th>CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>Epilation in 2-3 wk</td>
</tr>
<tr>
<td>10-15</td>
<td>Threshold for erythema; appears 18-20 days after exposure at lower doses; may appear within a few hours at higher doses</td>
</tr>
<tr>
<td>20</td>
<td>Moist desquamation, possible ulceration</td>
</tr>
<tr>
<td>25</td>
<td>Ulceration with slow healing</td>
</tr>
<tr>
<td>30-50</td>
<td>Blistering, necrosis at 3 wk</td>
</tr>
<tr>
<td>100</td>
<td>Blistering, necrosis at 1-2 wk</td>
</tr>
</tbody>
</table>


**Table 718-11**

<table>
<thead>
<tr>
<th>RADIONUCLIDE</th>
<th>THERAPEUTIC APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tritium</td>
<td>Dilution (force fluids)</td>
</tr>
<tr>
<td>Iodine-125 or iodine-131</td>
<td>Blockage (saturated solution of potassium iodide or potassium iodide), mobilization (antithyroid drugs)</td>
</tr>
<tr>
<td>Cesium-134 or cesium-137</td>
<td>Reduction of gastrointestinal absorption (Prussian blue)</td>
</tr>
<tr>
<td>Strontium-89 or strontium-90</td>
<td>Reduction of absorption (aluminum phosphate gel antacids), blockage (strontium lactate), displacement (oral phosphate), mobilization (ammonium chloride or parathyroid extract)</td>
</tr>
<tr>
<td>Plutonium and other transuranic elements</td>
<td>Chelation with zinc or calcium diethylenetriamine pentaacetic acid (investigational agents)</td>
</tr>
<tr>
<td>Unknown</td>
<td>Reduction of absorption (emetics, lavage, charcoal, or laxatives) in cases of ingestion</td>
</tr>
</tbody>
</table>

More than 85,000 new synthetic chemicals have been developed in the past 75 yr. Most did not previously exist in nature. These chemicals are used today in millions of products ranging from food packaging to clothing, building materials, motor fuels, cleaning products, cosmetics, medical products, toys, and baby bottles.

Synthetic chemicals are widely disseminated in the environment. The Toxic Release Inventory of the U.S. Environmental Protection Agency (EPA) reports that in 2011 more than 4 billion pounds of toxic chemicals were discharged to air, water, and land in the United States.

Human exposure to toxic synthetic chemicals is widespread. Children are especially likely to be exposed to the nearly 3,000 chemicals that are produced in amounts of 1 million pounds or more per yr. These are designated by the EPA as high-production-volume chemicals. Biomonitoring data on blood and urine levels of more than 200 high-production-volume chemicals are obtained annually by the Centers for Disease Control and Prevention in a sample of the U.S. population through the National Health and Nutrition Examination Survey. These data document that American children are exposed to a broad array of synthetic chemicals.

Toxic chemicals are being exported in ever-increasing quantities to the world’s poorer countries as these countries pass through industrial development. Environmental safeguards in those countries are typically not as stringent as in the industrially developed nations, and the potential for serious exposure to children there is therefore high.

**SYNTHETIC CHEMICALS AND HUMAN HEALTH**

Some synthetic chemicals have greatly benefitted human health. Antibiotics have helped control the major communicable diseases. Chemical disinfectants have reduced deaths from dysentery. Chemotherapeutic agents have made possible the cure of many childhood cancers.

But new chemicals have also been responsible for tragic episodes of disease, death, and environmental degradation. Many of these episodes have resulted in severe injury to children. A recurrent pattern has been that new chemicals were brought to market with great enthusiasm, were presumed harmless, and underwent little or no premarket safety testing. Then yr or decades later, after they had come into wide use, established markets, and become widely disseminated in the environment, the chemicals were found to have harmful effects.

Historical examples of synthetic chemicals that were initially hailed as beneficial but later found to cause great harm include thalidomide, a mild sedative that proved very effective at suppressing “morning sickness” in the 1st trimester of pregnancy, but later was found to have caused an epidemic of phocomelia in infants exposed in utero; tetraethyl lead, which was added to gasoline in the United States from the early 1930s until 1980 and was responsible for widespread lead poisoning with subclinical neurotoxicity and reduction in IQ across 2 generations of U.S. children (see Chapter 721); the pesticide dichlorodiphenyltrichloroethane (DDT), the environmental toxicity of which very nearly led to extinction of the osprey and the American bald eagle and that more recently was linked to increased risk for human breast cancer; the polychlorinated biphenyls (PCBs), highly persistent pollutants of which production was banned in 1977 but which continue today to contaminate major lakes and rivers and which have been found also to be responsible for loss of IQ and disruption of behavior in U.S. children; diethylstilbestrol (DES), which was administered to pregnant women to prevent miscarriage and later found to cause adenocarcinoma of the vagina in girls and young women who had been exposed in utero; and the ozone-destroying chlorofluorocarbons.

Other examples of synthetic chemicals that came into wide use with little assessment of their potential hazards include the phthalates, plasticizers widely used in plastics, cosmetics, and common household products, which are linked to increased risk for reproductive abnormalities in baby boys and to heightened risk of behavioral abnormalities that resemble attention-deficit/hyperactivity disorder (see Chapter 33); polybrominated diphenyl ethers, a class of chemicals widely used as flame retardants in carpets, furniture, and electronic equipment that are linked to persistent loss of intelligence and disruption of behavior; and bisphenol A, a plastics chemical that has been linked to neurodevelopmental disorders. These chemicals are all produced in volumes of millions of tons per yr, are widely disseminated in the environment, and are detectable in the bodies of nearly all Americans. Only now, decades after their introduction, are their possible hazards to children’s health beginning to be assessed.

**CHILDREN’S UNIQUE SUSCEPTIBILITY TO SYNTHETIC CHEMICALS**

The health effects of synthetic chemicals are especially serious when exposure occurs in early life—during pregnancy, in infancy, or in early childhood. Children are uniquely vulnerable to chemical pollutants for several reasons:

1. Children have proportionally greater exposures to many environmental pollutants than adults. Because they drink more water, eat more food, and breathe more air per kilogram of body weight, children are more heavily exposed to pollutants in water, food, and air. Children’s hand-to-mouth behavior and their play close to the ground further magnify their exposures.

2. Children’s metabolic pathways, especially in the 1st few mo after birth, are immature. Although in some instances children are better able than adults to cope with environmental toxicants because they are unable to metabolize them to their active form, children are frequently less able to detoxify and excrete chemical pollutants.

3. Infants and children are growing and developing, and their complex, fast-moving, and highly choreographed developmental processes are uniquely sensitive to disruption by chemical pollutants. Exposures to even minute doses of toxic chemicals during windows of exquisite vulnerability in early development have been shown to cause a wide array of diseases in childhood and also to increase risk for chronic disease and disability lifelong (Table 719-1).

4. Because children have many future years of life, they have time for the development of multistage chronic diseases that may be triggered by early exposures.
The unique susceptibility of infants and children to toxic chemicals—susceptibility that is both quantitatively and qualitatively different from that of adults—is summarized in the phrase "children are not little adults."

SAFETY TESTING OF SYNTHETIC CHEMICALS
A fundamental problem in environmental pediatrics is that only approximately 65% of high-production-volume chemicals have been tested for their potential hazards to human health, and fewer than 30% have been assessed for their pediatric or developmental toxicity. In the United States, chemicals are regulated under the 1976 Toxic Substances Control Act. Unfortunately, this law is obsolete, broken, and fails to protect children’s health against toxic synthetic chemicals.

At the time of its passage, the Toxic Substances Control Act was intended to be pioneering legislation that would require chemicals already in commerce to be tested for potential toxicity and that would also require premarket safety testing of all new chemicals. The Toxic Substances Control Act never fulfilled these noble intentions. A particularly egregious lapse was a decision by the Congress to “grandfather” 62,000 chemicals already on the market without any toxicity testing. In consequence of the failure of current chemical safety legislation, passed by the European Union in 2006, requires chemicals to be proven safe before they come to market and places the burden on industry to document chemical safety; there is no equivalent in the United States.

The EPA requires the manufacturers of 67 pesticide chemicals to determine whether these chemicals have the potential to disrupt the endocrine system. The results of this request for data led the EPA to develop a new Endocrine Disruptor Screening Program Comprehensive Management Plan that is analyzing the endocrine disrupting properties of chemical pesticides.

The United Nations Environment Programme (UNEP) is the agency within the United Nations that is responsible for the global management of chemicals. UNEP promotes chemical safety by providing information, policy advice, and technical guidance on toxic chemicals to developing and transitional countries. UNEP advocates for the establishment of international treaties to ban and control chemical substances. UNEP coordinates with other international organizations such as the Food and Agriculture Organization of the United Nations. UNEP has been centrally involved in partnership with the World Health Organization in coordinating the global effort to remove lead from gasoline in countries around the world.

SYNTHETIC CHEMICALS AND DISEASE IN CHILDREN
A large and growing body of evidence accumulated over the past 5 decades documents that chemical pollutants in the environment can cause disease and dysfunction in children. High-dose exposures can cause acute, clinically evident disease. Lower-dose exposures can cause subclinical injury—disease that is very real but undetectable only through special testing—such as decreases in intelligence, shortening of attention span, and disruption of behavior. When exposure to a chemical pollutant is widespread, subclinical toxicity can reduce intelligence and cause other adverse effects across entire societies (Fig. 719-1).

CHEMICAL POLLUTANTS OF MAJOR CONCERN
Air Pollutants
The outdoor air pollutants of greatest concern are photochemical oxidants (especially ozone), oxides of nitrogen, fine particulates, sulfur oxides, and carbon monoxide. These pollutants result principally from the combustion of fossil fuels. Automotive emissions are the major source of air pollution worldwide, followed by stationary sources such as coal-fired power plants and other industrial sources.

Elevated values of air pollutants, especially fine particulates, ozone, and oxides of nitrogen, are associated with respiratory problems in children, including decreased pulmonary expiratory flow, wheezing, and exacerbations of asthma. Fine particulate air pollution, even at low levels, is associated with slight increases in cardiopulmonary mortality and with an increased death rate from sudden infant death syndrome (see Chapter 375). A prospective cohort study of air pollution and lung development in California found an association between pollution and reduced lung growth from ages 10-18 yr, which leads to clinically significant decreases in lung function that persist into adulthood. It is notable that these effects were seen at air toxic levels below the National Ambient Air Quality Standards set by the EPA under the Clean Air Act.

Indoor air also can be an important source of respiratory irritation, because many children spend 80-90% of their time indoors. Globally, indoor air pollution is largely caused by household use of solid fuel, such as wood, charcoal, or dung. According to the World Health Organization, globally more than 2 million children < age 5 yr die each year from acute respiratory infections of which 50% are attributable to the indoor burning of biomass fuels. Indoor air pollution has become especially important in the United States since the energy crises of the 1970s, which led to the construction of tighter, more energy-efficient homes. Second-hand cigarette smoke is an especially hazardous constituent of indoor air and a powerful asthma trigger. Allergens in indoor air can contribute to respiratory problems and include cockroach, mite, mold, and cat and dog allergens.

<table>
<thead>
<tr>
<th>CHEMICAL POLLUTANT</th>
<th>EFFECT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air pollution</td>
<td>Asthma, other respiratory diseases, sudden infant death syndrome</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Mesothelioma and lung cancer</td>
</tr>
<tr>
<td>Benzene, nitrosamine, vinyl chloride, ionizing radiation</td>
<td>Cancer</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>Adenocarcinoma of the vagina after intrauterine exposure</td>
</tr>
<tr>
<td>Environmental tobacco smoke</td>
<td>Increased risk of sudden infant death syndrome and asthma</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>Fetal alcohol syndrome after intrauterine exposure</td>
</tr>
<tr>
<td>Lead</td>
<td>Neurobehavioral toxicity from low-dose exposure</td>
</tr>
<tr>
<td>Methyl mercury</td>
<td>Developmental neurotoxicity</td>
</tr>
<tr>
<td>Organophosphate insecticides</td>
<td>Developmental neurotoxicity</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>Developmental neurotoxicity</td>
</tr>
<tr>
<td>Polybrominated diphenyl ethers</td>
<td>Developmental neurotoxicity</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Developmental neurotoxicity and reproductive impairment</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Phocomelia after intrauterine exposure</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>Elevated risk of leukemia after intrauterine exposure</td>
</tr>
</tbody>
</table>
Oil Spill Hazards

Through 2014, there have been at least 36 crude oil spills worldwide. Ten of these spills have occurred since 1980, the largest in 2010. Although specific composition and concentrations vary, crude oil contains many toxic chemicals that are of concern to human health, including metals (e.g., zinc, cadmium, and lead) (see Chapters 720 and 721), volatile organic compounds (including benzene, toluene, ethyl benzene, and styrene), and semivolatile organics (such as polycyclic aromatic compounds). Several of these compounds are classified as possible or potential carcinogens, endocrine disruptors, and neurotoxins. Chemical dispersants—mixtures of detergents and organic solvents—are often used to break up spilled oil and may also have potential adverse effects on health. Toxic effects may occur from exposure during contact with the skin, eyes, or respiratory tract or in a person's diet (e.g., drinking of contaminated water or eating of contaminated seafood).

Commonly reported symptoms from direct exposure to crude oil include eye redness and burning, rashes, sore throat, respiratory difficulty, and acute neurologic symptoms such as headache and nausea. Children with asthma may be particularly vulnerable to respiratory toxicity. The amount and duration of exposure along with individual genetic variability influence the degree of symptoms.

Most information on health effects of oil spills comes from studies of exposed adult workers; there are few studies of health effects, acute or long term, in children. Studies of workers exposed to spilled oil have noted elevated blood concentrations of heavy metals such as lead and cadmium, evidence of genotoxic effects, and endocrine disruption (as manifested by changes in prolactin and cortisol levels). Children and teens are at risk for exposure in a variety of settings, including recreational activities like swimming and boating as well as clean-up efforts. Children should not be allowed to play in or around areas where the water or beach contains oil or sludge. In light of teenagers’ propensity to not adhere as well as adults to workplace safety regulations, teens should not be directly involved in spill clean-up efforts.

Lead

See Chapter 721.

Mercury

See Chapter 720.

Asbestos

Between 1947 and 1973, asbestos was sprayed as insulation on classroom walls and ceilings in approximately 10,000 schools in the United States. Subsequent deterioration of this asbestos has released asbestos fibers into the air. Asbestos is not a health hazard so long as it is intact, but once it becomes airborne, it can be inhaled by children to produce adverse health effects. Asbestos is a human carcinogen, and the 2 principal cancers caused by asbestos are lung cancer and mesothelioma. U.S. federal law requires that all schools be inspected periodically for asbestos and that the results be made public. Removal is required only when asbestos is visibly deteriorating or is within the reach of children. In most cases, placement of barriers (drywall walls or drop ceilings) provides appropriate protection.

Second-Hand Tobacco Smoke

Smoking during pregnancy poses a hazard to the fetus (see Chapter 96). Infants born to women who smoke are, on average, 10% smaller than infants born to nonsmoking women. Infants of parents who smoke have a higher risk of sudden infant death syndrome. Nicotine from tobacco smoke appears to be a developmental neurotoxin.

Second-hand smoke exposure is also a hazard to children. The United States has made substantial progress in reducing exposure to second-hand smoke over the last 15 yr and serum cotinine levels have declined by 70% in U.S. nonsmokers of all ages. Children <1 yr old continue to have mean cotinine levels twice those of adults, highlighting their unique vulnerability. Children exposed to second-hand tobacco smoke have increased frequency of lower respiratory illness, more middle-ear effusions, and more viral respiratory illnesses than unexposed children.

Pesticides

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and rodents. Approximately 600 pesticides are registered with the EPA for use in the United States. Diet is a major route of children’s exposure to pesticides, because children are exposed to residues of multiple pesticides on fruit and vegetables, especially fruits and vegetables imported from countries where pesticide use is heavier than in the United States. Children also may be exposed in homes or schools, on lawns, and in gardens. They may be exposed to pesticide drift from agricultural areas that have been sprayed. Children employed in agriculture or living in migrant farm camps are at risk of direct exposure to many pesticides.

Children can be acutely overexposed to pesticides. High-dose exposure to both organophosphates and carbamate pesticides can cause acute neurotoxicity. Both of these classes of pesticides act through inhibition of acetylcholinesterase and are responsible for the largest number of acute poisoning cases. Symptoms include meiosis (although not in all cases), excess salivation, abdominal cramping, vomiting,
diarrhea, and muscle fasciculation. In severe cases, the child may experience loss of consciousness, cardiac arrhythmias, and death by respiratory arrest. The war gas sarin is an organophosphate. See Chapter 63 for treatment of poisoning from drugs, chemicals, and plants.

Pesticides can also cause a range of chronic toxic effects: polynuropathy and central nervous system dysfunction (organophosphates); hormonal disruption and reproductive impairment (DDT, kepone, dichloroethane); cancer (aldrin, dieldrin, chlorophenoxy herbicides [2,4,5-T]); and pulmonary fibrosis (parquat). Prenatal exposure to organophosphate pesticides at levels that produce no evident toxicity in pregnant women has been associated with neurodevelopmental disability in children, with reduction in IQ and disordered executive function.

Children’s exposures to pesticides can be reduced by minimizing applications to lawns, gardens, schools, and playgrounds; adapting techniques of integrated pest management; and reducing pesticide applications to food crops. Consumption of organic produce dramatically reduces organophosphate pesticide exposure in school-age children. Exposure to herbicides may increase due to an EPA decision to expand their use in agriculture.

**Polychlorinated Biphenyls, DDT, Dioxins, Brominated Flame Retardants, and Other Halogenated Hydrocarbons**

Chlorinated hydrocarbons are used as insecticides (DDT), plastics (polyvinyl chloride), electrical insulators (PCBs), and solvents (trichloroethylene). High levels of dioxins and furans are formed during synthesis of chlorinated herbicides or as by-products of plastic combustion. All of these materials are widely dispersed in the environment. Brominated flame retardants are used in carpets, furniture, and computers. DDT, PCBs, and dioxins are highly persistent.

The embryo, fetus, and young child are at particularly high risk of injury from halogenated hydrocarbons. All of these compounds are lipid-soluble. They readily cross the placenta, and they accumulate in breast milk. Intrauterine exposure to PCBs and brominated flame retardants has been linked to persistent neurobehavioral dysfunction in children.

Fish from contaminated waters are a major source of children’s exposure to PCBs. Children can be exposed in utero or through breast milk. To protect children and pregnant women in the United States against PCBs in fish, government agencies have issued advisories concerning fish consumption for certain lakes and rivers. Combustion of medical waste containing polyvinyl chloride and the use of chlorine to bleach paper products are major preventable sources of environmental dioxin and should be discouraged. Older fluorescent lightballasts that were installed decades ago in schools in the United States are another source of PCB exposure. PCB-containing ballasts should be removed from schools as soon as possible to prevent environmental contamination. Removal must be performed by trained workers.

**Endocrine Disruptors**

A number of chemicals have been shown to adversely affect the endocrine systems of animals and humans, including DES, DDT, PCBs, and dioxins. Other chemicals, such as other pesticides and phthalates (plasticizers), are also suspected of possessing endocrine disruptor effects. Phthalates have been associated with obesity in animal experiments. Higher urinary levels of bisphenol A are associated with obesity-related outcomes, such as cardiovascular disease, in a cross-sectional analysis of the National Health and Nutrition Examination Survey 2003-2004 data in adults. The many effects of endocrine disruptors on wildlife include eggshell thinning in birds, sterility in seals, feminization and cryptorchidism in panthers, and low hatching rates in alligators. In humans, endocrine disruption is implicated in the epidemiologic observations of a trend toward earlier thelarche and menarche in girls (see Chapter 14), the rising rates of testicular cancer and hypospadias, and diminishing sperm counts. The most clearly observed effects include adenocarcinoma of the vagina in women and cryptorchidism in men whose mothers took DES and shortening of the anogenital distance, a measure of in utero feminization, in baby boys whose mothers had elevated exposures to phthalates during pregnancy. The presence of elevated concentrations of plasma phthalate esters is associated with early thelarche in Puerto Rican girls. Some endocrine disruptors may also have adverse effects on brain development. Prenatal exposure to low-molecular-weight phthalates is associated with shortening of attention span in children 4-9 yr old.

**Environmental Carcinogens**

Children may be exposed to carcinogenic pollutants in utero or after birth. Children appear more sensitive than adults to certain chemical carcinogens and also to ionizing radiation (see Chapter 718). The potential for in utero carcinogenesis was first recognized with the discovery that clear cell adenocarcinoma of the vagina could develop in women after intrauterine exposure to DES.

Carcinogenesis also may be associated with exposures in the home and community. Children of asbestos workers and children who have grown up near asbestos plants have been found to have a higher incidence of mesothelioma than unexposed populations. Children who grow up on farms have elevated rates of leukemia; pesticides are suspected of playing an etiologic role. Intrauterine exposure to trichloroethylene via contaminated drinking water has been associated with an increased incidence of leukemia among girls living near an industrial facility and industrial waste site.

**Routes of Exposure**

**Transplacental.** Heavy metals such as lead and mercury, fat-soluble compounds such as PCBs and DDT, and endocrine disruptors such as phthalates readily cross the placenta. They may have serious and irreversible toxic effects on the developing nervous, endocrine, and reproductive organs, even at very low levels.

**Water.** Approximately 200 chemicals have been found in various amounts in water supplies. Lead is especially common. In some older neighborhoods, lead in water derives from lead pipes. More commonly, it is dissolved (leached) by soft, acidic water from lead-containing solder. The highest levels of lead occur in water that has been standing in pipes overnight. It is wise therefore to run water for 2-3 min each morning before making up infant formula. Solvents and components of gasoline such as methyl tertiary-butyl ether and benzene are commonly encountered in groundwater. Herbicides, like atrazine, are commonly found contaminants in drinking water in agricultural areas.

**Air.** Vehicular emissions are the major source of urban air pollution. Diesel exhaust is a human carcinogen. In rural areas, wood smoke can contribute to air pollution. Children living in the vicinity of smelters and chemical production plants can be exposed to toxic industrial emissions such as lead, benzene, and 1,3-butadiene.

**Food.** Many chemicals are intentionally added to food to improve appearance, taste, texture, or preservation, but many such chemicals have been poorly tested for potential toxicity. Residues of many pesticides are found in both raw and processed foods. Levels of pesticides are lower in organic produce than in conventionally grown fruits and vegetables. Children who consume organic produce have substantially lower urinary pesticide levels than children who eat conventional produce.

**Work Clothes.** Illness in children sometimes may be traced to contaminated dust from parents’ work clothes; toxicity from lead, beryllium, dioxin, organophosphate pesticides, and asbestos has occurred. Such exposure (termed “fouling the nest”) can be prevented by providing facilities at work for changing and showering.

**Schools.** Children may be exposed in schools, kindergartens, and nurseries to lead paint, molds, asbestos, environmental tobacco smoke, pesticides, and hazardous arts and crafts materials. Substantial opportunities for prevention exist in the school environment, and pediatricians are often consulted for advice.

**Child Labor.** Four to 5 million children and adolescents in the United States work for pay, and child labor is widespread around the world. Working children are at high risk of physical trauma and injury. They also may be exposed to a wide range of toxic chemicals, including
pesticides in agriculture and lawn work, asbestos in construction and building demolition, and benzene in pumping gasoline.

**THE PHYSICIAN’S ROLE**

Pediatricians have time and again played key roles in the initial recognition of diseases caused by toxic chemicals. Every pediatrician needs to be an “alert clinician” ever open to the possibility of discovering new diseases in children caused by exposures in the environment. In considering the origins of noninfectious disease, pediatricians should ask about the home environment, parental occupation, unusual exposures, and neighborhood factories. An environmental cause is particularly likely when several unusual cases of disease or constellations of findings occur together. Any adolescent with a traumatic injury may have been injured at work.

The history is the single most important instrument for obtaining information on environmental exposures. Information about current and past exposures (including questions about work and travel to or residence in developing countries) should be sought routinely on every new patient and on every patient with illness of unclear causation through a few brief screening questions. Changes in patterns of exposure or new exposures may be especially important. If suspicious information is elicited, more detailed follow-up should be pursued. Referral to a pediatric environmental health specialty unit may be indicated (http://aoec.org/PEHSU/index.html). Accurate diagnosis of an environmental cause of disease can lead to better care of sick children and prevention of disease in other children.

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Chapter 719  Chemical Pollutants  3427.e1

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Lead, mercury, arsenic, and cadmium, 4 of the World Health Organization’s (WHO) “10 chemicals of greatest public health concern,” are the heavy metals posing the greatest threats to humans. The most prevalent of these exposures is lead (see Chapter 721). This chapter discusses mercury and arsenic.

Heavy metal intoxication results in diverse multiorgan toxicity through widespread disruption of vital cellular functions. A meticulous history of environmental exposure may be necessary to correctly identify heavy metals as the source of the protein manifestations associated with such exposure. Arsenic exposure can occur from contaminated food or water; globally, more than 100 million people are estimated to be chronically exposed to drinking water containing high arsenic levels. Mercury exposure occurs primarily through food; fish is a major source of methyl mercury exposure.

**ARSENIC**

**Epidemiology**

Arsenic is a metalloid that exists in 4 forms: elemental arsenic, arsine gas, inorganic arsenic salts (pentavalent arsenate form or trivalent arsenite form), and organic arsenic compounds. Toxic manifestations are higher in the more soluble and higher-valence compounds. **Arsine gas** is the most toxic form of arsenic. Mass poisonings from exposure to arsenic have occurred throughout history, including one in 1998 in Wakayama, Japan, in which 70 people were poisoned. Children may be poisoned after exposure to inorganic arsenic found in pesticides, herbicides, dyes, homeopathic medicines, and certain contaminated folk remedies from China, India, and Southeast Asia (see Chapter 64). Soil deposits contaminate artesian well water. Groundwater contamination with arsenic is a common problem in developing countries and has been reported to be a common well contaminant in Alaska, Maine, North Carolina, and areas in western United States. Food products (e.g., rice, organic brown rice syrup, fruit juices) cooked in contaminated water may actually absorb arsenic, thus concentrating it in the food. The WHO has set 10 µg/L as the upper limit of safety. In many parts of Asia and South America, this limit is frequently exceeded. Arsenic concentrations in one quarter of the wells in Bangladesh exceed 50 µg/L and 35-77 million of the 125 million inhabitants of Bangladesh regularly consume arsenic-contaminated water. Occupational exposure may occur in industries involved in the manufacturing, mining, smelting, or refining of glass, pottery, electronic and semiconductor components, and lasers. Although arsenic is no longer produced in the United States, it is produced in many countries and is imported into the United States for industrial use. Organic arsenic compounds may be found in seafood, pesticides, and some veterinary pharmaceuticals. In contrast to mercury, the organic forms of arsenic found in seafood are nontoxic.

**Pharmacokinetics**

Elemental arsenic is insoluble in water and bodily fluids and, therefore, is insignificantly absorbed and nontoxic. Inhaled arsine gas is rapidly absorbed through the lungs. The inorganic arsenic salts are well absorbed through the gastrointestinal tract, lungs, and skin. The organic arsenic compounds are well absorbed through the gastrointestinal tract. After acute exposure, arsenic initially is bound to the protein portion of hemoglobin in the red blood cells (RBCs) and rapidly distributed to all tissues. Inorganic arsenic is methylated and is eliminated predominantly by the kidneys, with approximately 95% excreted in the urine and 5% excreted in the bile. Most of the arsenic is eliminated in the 1st few days, with the remainder slowly excreted over a period of several weeks. Arsenic concentrates in hair, nails, and skin. Measurement of the distance of Mees lines (transverse white striae on the nail) from the nail bed can provide an estimate of time of exposure (nails grow at the rate of 0.4 mm/day).

**Pathophysiology**

After exposure to arsine gas, absorbed arsine enters RBCs and is oxidized to arsenic dihydride and elemental arsenic. Complexing of these derivatives with red cell sulfhydryl groups results in cell membrane instability and massive hemolysis. The inorganic arsenic salts poison enzymatic processes vital to cellular metabolism. Trivalent arsenic binds to sulfhydryl groups, resulting in decreased production of adenosine triphosphate through the inhibition of enzyme systems such as the pyruvate dehydrogenase and α-ketoglutarate complexes. Pentavalent arsenic may be biotransformed to trivalent arsenic or substituted for phosphate in the glycolytic pathway, resulting in uncoupling of oxidative phosphorylation.

**Clinical Manifestations**

Arsine gas is colorless, odorless, nonirritating, and highly toxic. Inhalation causes no immediate symptoms. After a latent period of 2-24 hr, exposed individuals experience massive hemolysis, malaise, headache, weakness, dyspnea, nausea, vomiting, abdominal pain, hepatomegaly, pallor, jaundice, hemoglobinuria, and renal failure (Table 720-1). Acute ingestion of arsenic produces gastrointestinal toxicity within minutes to hours and is manifested as nausea, vomiting, abdominal pain, and diarrhea. Hemorrhagic gastroenteritis with extensive fluid loss and third spacing may result in hypovolemic shock. Cardiovascular toxicity includes QT interval prolongation, polymorphous ventricular tachycardia, congestive cardiomyopathy, pulmonary edema, and cardiogenic shock. Acute neurologic toxicity includes delirium, seizures, cerebral edema, encephalopathy, and coma. Lethal doses of arsenates are 5-50 mg/kg; lethal doses of arsenites are <5 mg/kg.

**Late sequelae** include hematuria, proteinuria, and acute tubular necrosis. A delayed sensorimotor peripheral neuropathy may appear days to weeks after acute exposure, secondary to axonal degeneration. Neuropathy manifests as painful dysesthesias followed by diminished vibratory, pain, touch, and temperature sensation; decreased deep tendon reflexes; and, in the most severe cases, an ascending paralysis with respiratory failure mimicking Guillain-Barré syndrome (see
Chapter 616. Adult survivors of infant arsenic poisoning experience higher mortality from disorders of the nervous system compared to adults without such exposure.

**Subacute toxicity** is characterized by prolonged fatigue, malaise, weight loss, headache, chronic encephalopathy, peripheral sensorimotor neuropathy, leukopenia, anemia, thrombocytopenia, chronic cough, and gastroenteritis. Mees lines in the nails become apparent 1-2 mo after exposure in approximately 5% of patients. Dermatologic findings include alopecia, oral ulceration, peripheral edema, a pruritic macular rash, and desquamation.

Chronic arsenic toxicity causes significant morbidity in children resulting in skin lesions, lung disease, and defect in intellectual function. **Chronic exposure** to low levels of arsenic is usually from environmental or occupational sources. Over the course of years, dermatologic lesions develop, including hyperpigmentation, hypopigmentation, hyperkeratoses (especially on the palms and soles), squamous and basal cell carcinomas, and **Bowen disease** (cutaneous squamous cell carcinoma in situ). Encephalopathy and peripheral neuropathy may be present. Hepatomegaly, hypersplenism, noncirrhotic portal fibrosis, and portal hypertension occur. **Blackfoot disease** is an obliterator arterial disease of the lower extremities associated with chronic arsenic exposure that has been described in Taiwan. Carcinogenicity of chronic arsenic exposure is reflected in increased rates of cancers of the skin, lung, liver, bladder, and kidney as well as of angiosarcomas. The effects of prenatal exposure to arsenic are uncertain but may include low birthweight.

### Laboratory Findings

The diagnosis of arsenic intoxication is based on characteristic clinical findings, a history of exposure, and elevated urinary arsenic values, the last of which confirm the exposure. A spot urine arsenic level should be determined for symptomatic patients before chelation, although initially the result may be negative. Because urinary excretion of arsenic is intermittent, definitive diagnosis depends on a 24 hr urine collection. Concentrations greater than 50 µg/L in a 24 hr urine specimen are consistent with arsenic intoxication (Table 720-2). Urine specimens must be collected in metal-free containers. Ingestion of seafood containing nontoxic arsenobetaine and arsenocholine can cause elevations of urinary arsenic. Blood arsenic levels rarely are helpful because of their high variability and the rapid clearance of arsenic from the blood in acute poisonings. Elevated arsenic values in the hair or nails must be interpreted cautiously because of the possibility of external contamination. Abdominal radiographs may demonstrate ingested radiopaque arsenic.

Later in the course of illness, a complete blood cell count may show anemia, thrombocytopenia, and leukopenia, followed by leukocytosis and eosinophilia and basophilic stippling of RBCs. The serum concentrations of creatinine, bilirubin, and transaminases may be elevated; urinalysis may show proteinuria, pyuria, and hematuria; and examination of the cerebrospinal fluid may show protein elevations.

### MERCURY

#### Epidemiology

Mercury exists in 3 forms: elemental mercury, inorganic mercury salts, and organic mercury (Table 720-3). **Elemental mercury** is present in thermometers, sphygmomanometers, barometers, batteries, and some medicinal preparations. Dental amalgams containing elemental mercury release trace amounts of mercury. An expert panel for the National Institutes of Health concluded that existing scientific evidence does not indicate that dental amalgams pose a health risk and should not be replaced merely to decrease mercury exposure. A 2009 WHO expert panel concluded that a global near-term ban on amalgam would be problematic for public and dental health. However, this committee recommended that alternatives to amalgam should be sought as part of a phase-out of the use of mercury-containing amalgams.

**Inorganic mercury salts** are found in pesticides, disinfectants, anti-septics, pigments, dry batteries, and explosives and are preservatives in some medicinal preparations. **Organic mercury** in the diet, especially fish containing methyl mercury, is a major source of mercury exposure among the general population. Industries that may produce mercury-containing effluents include chlorine and caustic soda production, mining and metallurgy, electroplating, chemical and textile manufacturing, paper and pharmaceutical manufacturing, and leather tanning. Mercury compounds in the environment are methylated to methyl.

### Table 720-1

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>EFFECTS OF ARSENIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal system</td>
<td>Submucosal vesicles, watery or bloody diarrhea, severe hematemesis</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Vasodilation, hypotension</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Hematuria, proteinuria, acute tubular necrosis</td>
</tr>
<tr>
<td>Hematologic and lymphatic system</td>
<td>Anemia and thrombocytopenia; acute hemolysis with arsenic gas</td>
</tr>
<tr>
<td>Liver</td>
<td>Fatty degeneration with central necrosis</td>
</tr>
<tr>
<td>Skin</td>
<td>Desquamation, alopecia, hyperkeratosis, nail changes</td>
</tr>
<tr>
<td>Teratogenic</td>
<td>Neural tube defects in the fetus</td>
</tr>
<tr>
<td>Oncologic</td>
<td>Urologic cancer, other malignancies</td>
</tr>
</tbody>
</table>

### Table 720-2

<table>
<thead>
<tr>
<th></th>
<th>ARSENIC</th>
<th>MERCURY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>74.9 Da</td>
<td>200.59 Da</td>
</tr>
<tr>
<td>Acceptable blood level</td>
<td>&lt;5 µg/L (&lt;0.665 nmol/L)</td>
<td>&lt;10 µg/L (&lt;50 nmol/L)</td>
</tr>
<tr>
<td>Acceptable urine level</td>
<td>&lt;50 µg/L (&lt;6.65 nmol/L) 24 hr urine sample</td>
<td>&lt;20 µg/L (&lt;100 nmol/L)</td>
</tr>
<tr>
<td>Intervene at blood level</td>
<td>&gt;35 µg/L (&gt;175 nmol/L)</td>
<td></td>
</tr>
<tr>
<td>Intervene at urine level</td>
<td>&gt;100 µg/L (&gt;13.3 nmol/L) 24 hr urine sample</td>
<td>&gt;150 µg/L (&gt;750 nmol/L)</td>
</tr>
</tbody>
</table>
mercury by soil and water microorganisms. Methyl mercury in the water rapidly accumulates in fish (swordfish, king mackerel, fresh tuna, tile fish, shark) and other aquatic organisms, which are in turn consumed by humans. To address concerns that maternal consumption of large quantities of fish during pregnancy may expose the fetus to concentrations of mercury with adverse consequences, the longitudinal Seychelles Child Development Study has been ongoing since the late 1980s. The first cohort of the study involved nearly 800 mother–child pairs, with subsequent cohorts enrolled. Despite a high maternal fish intake (mean of 12 fish meals per wk), follow-up of children at least through 9 yr of age has revealed no consistent adverse developmental effects. Well-known large outbreaks of methyl mercury intoxication include the incidents in Japan in the 1950s (Minamata disease, from consumption of contaminated seafood) and in Iraq in 1971 (from consumption of grain treated with a methyl mercury fungicide).

**Thimerosal** is a mercury-containing preservative used in some vaccines. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. During an ongoing review of biologic products in response to the U.S. Food and Drug Administration (FDA) Modernization Act of 1997, the FDA determined that infants who received thimerosal-containing vaccines at multiple visits might have been exposed to more mercury than recommended by federal guidelines. As a precautionary measure, the American Academy of Pediatrics, American Academy of Family Physicians, Advisory Committee on Immunization Practices, and U.S. Public Health Service issued a joint recommendation in 1999 that thimerosal be removed from vaccines as quickly as possible. In the United States, thimerosal has been removed from all vaccines in the recommended childhood immunization schedule. Infants and children who have received thimerosal-containing vaccines do not need to undergo blood, urine, or hair testing for mercury because the concentrations of mercury would be quite low and would not require treatment. The benefits and risks of vaccines containing thimerosal should be discussed with parents (as with all vaccines). The larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines. Studies do not demonstrate a link between thimerosal-containing vaccines and autistic spectrum disorders (see Chapter 30.1), and no evidence supports a change in the standard of practice with regard to administration of thimerosal-containing vaccines in areas of the world where they are used. A rise in blood mercury levels following a single dose of hepatitis vaccine was seen in preterm infants, but the clinical significance is unknown.

**Pharmacokinetics**

Inhaled elemental mercury vapor is 80% absorbed by the lungs and is distributed rapidly to the central nervous system because of its high lipid solubility. The elemental mercury is oxidized by catalase to the mercuric ion, which is the reactive form that causes cellular toxicity. Elemental mercury liquid is poorly absorbed from the gastrointestinal tract, with less than 0.1% being absorbed. The half-life of elemental mercury in the tissues is approximately 60 days, most of the excretion occurring in the urine.

Inorganic mercury salts are approximately 10% absorbed from the gastrointestinal tract and cross the blood–brain barrier to a lesser extent than elemental mercury. Mercuric salts are more soluble than mercurous salts and, therefore, produce greater toxicity. Elimination occurs primarily in the urine, with a half-life of approximately 40 days.

**Methyl mercury** is the most avidly absorbed of the organic mercury compounds, with approximately 90% absorbed from the gastrointestinal tract. The lipophilic, short-chain alkyl structure of methyl mercury allows it to distribute rapidly across the blood–brain barrier and placenta. Methyl mercury is approximately 90% excreted in the bile, with the remainder being excreted in the urine. The half-life is 70 days.

### Table 720-3 Differential Characteristics of Mercury Exposure

<table>
<thead>
<tr>
<th>ELEMENTAL</th>
<th>INORGANIC (SALT)</th>
<th>ORGANIC (ALKYL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary route of exposure</td>
<td>Inhalation</td>
<td>Oral</td>
</tr>
<tr>
<td>Primary tissue distribution</td>
<td>CNS, kidney</td>
<td>Kidney</td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal, GI</td>
<td>Renal, GI</td>
</tr>
<tr>
<td>Clinical effects:</td>
<td>CNS</td>
<td>Tremor, erythema (irritability)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>+++</td>
<td>—</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>+</td>
<td>+++ (caustic)</td>
</tr>
<tr>
<td>Renal</td>
<td>+</td>
<td>+++ (acute tubular necrosis)</td>
</tr>
<tr>
<td>Acrodynia</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Therapy</td>
<td>BAL, DMSA</td>
<td>BAL, DMSA</td>
</tr>
</tbody>
</table>

BAL, British antilewisite; CNS, central nervous system; DMSA, 2,3-dimercaptopropanoic acid; GI, gastrointestinal; +, mild; ++, moderate; +++, severe.

gingivostomatitis. The syndrome may result from long-term exposure to elemental mercury, inorganic mercury salts, or certain organic mercury compounds, all of which may be metabolized to mercuric ions. The tremor starts as a fine intention tremor of the fingers that is abolished during sleep but that may later involve the face and progress to choreoathetosis and spasmatic ballismus. Mixed sensorimotor neuropathy and visual disturbances may also be present. The neuropsychiatric disturbances include emotional lability, delirium, headaches, memory loss, insomnia, anorexia, and fatigue. Renal dysfunction ranges from asymptomatic proteinuria to nephrotic syndrome.

**Acrodynia, or pink disease,** is a rare idiosyncratic hypersensitivity reaction to mercury that occurs predominantly in children exposed to mercury powders. The symptom complex includes generalized pain, paresthesias, and an acral (hands, feet) rash that may spread to involve the face. The rash typically is red-pink, papular, pruritic, and painful; it may progress to desquamation and ulceration. Morbilliform, vesicular, and hemorrhagic variants have been described. Other important features include anorexia, apathy, photophobia, and hypotonia, especially of the pectoral and pelvic girdles. Irritability, tremors, diaphoresis, insomnia, hypertension, and tachycardia may be present. Some cases initially were diagnosed as pheochromocytoma. The outcome is good after removal of the source of mercury exposure.

**Methyl mercury intoxication** (also known as Minamata disease after the widespread mercury poisoning that occurred at Minamata Bay in Japan in people who had ingested contaminated fish) manifests as delayed neurotoxicity that appears after a latent period of weeks to mo. It is characterized by ataxia; dysarthria; paresthesias; tremors; movement disorders; impairment of vision, hearing, smell, and taste; memory loss; progressive dementia; and death. Infants exposed in utero are the most severely affected, with low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures. Although there is significant residual morbidity from methyl mercury neurotoxicity, observations on long-term follow-up of children exposed in Iraq reveal complete or partial resolution in most cases.

### Laboratory Findings

The diagnosis of mercury intoxication is based on characteristic clinical findings, the history of exposure, and elevation of whole blood or urine mercury values, the last of which confirms the exposure. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Blood should be collected in special tubes for trace elements from laboratories that are capable of performing those tests. Levels <10 µg/L in whole blood and <20 µg/L in a 24 hr urine specimen are considered normal (see Table 720-2). Although blood mercury levels may reflect acute exposure, they decrease as mercury redistributes into the tissues. Urine mercury levels are most useful for identifying long-term exposures, except in the case of methyl mercury, which undergoes minimal renal excretion. Urinary mercury levels are used in monitoring efficacy of chelation therapy, whereas blood levels are used primarily in monitoring organic mercury poisonings. Hair analysis for mercury is not reliable because hair reflects both endogenous and exogenous mercury exposure (hair avidly binds mercury from the environment). Abdominal radiographs may demonstrate ingested radiopaque mercury.

Urinary markers of early nephrotoxicity include microalbuminuria, retinol-binding protein, β2-microglobulin, and N-acetyl-β-D-glucosaminidase. Early neurotoxicity may be detected with neuropsychiatric testing and nerve conduction studies, whereas severe central nervous system toxicity is apparent on CT or MRI.

### Treatment of Arsenic and Mercury Intoxication

The principles of management for arsenic and mercury intoxication include prompt removal from the source of poisoning, aggressive stabilization and supportive care, decontamination, and chelation therapy when appropriate. Once the diagnosis is suspected, the local poison control facility should be contacted, and care coordinated with physicians who are familiar with the management of heavy metal poisoning.

Supportive care for patients exposed to arsine gas requires close monitoring for signs of hemolysis, including evaluation of the peripheral blood smear and urinalysis. Transfusion of packed RBCs may be necessary, as may administration of intravenous fluids, sodium bicarbonate, and mannitol to prevent renal failure secondary to the deposition of hemoglobin in the kidneys. After inhalation of elemental mercury vapor, patients require careful monitoring of respiratory status, which may include pulse oximetry, arterial blood gas analysis, and chest radiography. Supportive care involves administration of supplemental oxygen and, in severe cases, intubation and mechanical ventilation.

Acute ingestion of inorganic arsenic and mercury salts results in hemorrhagic gastroenteritis, cardiovascular collapse, and multiorgan dysfunction. Fluid resuscitation, pressor agents, and transfusion of blood products may be required for management of cardiovascular instability. Severe respiratory distress, coma with loss of airway reflexes, intractable seizures, and respiratory paralysis are indications for intubation and mechanical ventilation. Renal function must be monitored carefully for signs of renal failure and the need for hemodialysis.

Gastrointestinal decontamination after ingestion of the inorganic arsenic and mercury salts has not been well studied. Because of the corrosive effects of these compounds, induced emesis is not recommended, and endoscopy may be considered before gastric lavage. Arsenic and mercury are not well adsorbed to activated charcoal, but its use may be helpful if coingestants are suspected. Whole-bowel irrigation is used to remove any radiopaque material remaining in the gastrointestinal tract.

**Chelation** for acute arsenic and mercury poisoning is most effective when administered as soon as possible after the exposure. Chelation should be continued until 24 hr urinary arsenic or mercury levels return to normal (<50 µg/L for arsenic and <20 µg/L for mercury), the patient is symptom-free, or the remaining toxic effects are believed to be irreversible. The efficacy of chelation in long-term exposures is reduced because heavy metal in the tissue compartment is relatively unexchangeable and some degree of irreversible toxicity has already occurred.

**Dimercaprol,** also known as 2,3-dimercaptopropanol or British antilewisite (BAL), is the chelator of choice for a patient who cannot tolerate oral therapy, as often is true for critically ill patients and after ingestion of the corrosive inorganic arsenic and mercury salts. BAL is available suspended in peanut oil and benzyl benzoate in 3 mL ampules at a concentration of 100 mg/mL for deep intramuscular (IM) injection. For **arsenic poisoning,** the recommended regimen of BAL is 2.5 mg/kg IM q6h for the 1st 2 days, 2.5 mg/kg IM q12h on the 3rd day, and then 2.5 mg/kg/day IM for 10 days. For severe arsenic poisoning, the dose of BAL is increased to 3 mg/kg IM q4h for 2 days, 3 mg/kg IM q6h on day 3, and then 3 mg/kg IM q12h for 10 days. The dose of BAL for **inorganic mercury poisoning** is 5 mg/kg IM on the 1st day, and then 2.5 mg/kg IM q12-24h for 10 days. The BAL–heavy metal complex is excreted in the urine and bile. A period of 5 days between courses of chelation is recommended. Adverse effects of BAL include pain at the injection site, hypertension, tachycardia, diaphoresis, nausea, vomiting, abdominal pain, a burning sensation in the oropharynx, and a feeling of constriction in the chest. BAL may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals. It is important to note that BAL is contraindicated for chelation of methyl mercury because BAL redistributes methyl mercury to the brain from other tissue sites, resulting in increased neurotoxicity.

**D-Penicillamine** is an orally administered chelator that can be considered for less-severe mercury poisoning or as an adjunct to BAL therapy in arsenic poisoning, but its use is largely restricted because of the potential for significant leukopenia, thrombocytopenia, and proteinuria. A newer investigational analog, N-acetyl-d-l-penicillamine, is used with variable success in mercury poisoning.

Oral chelating agents are used to replace the painful BAL injections when the patient is stable enough to tolerate oral therapy and prolonged chelation is necessary. **Succimer,** also known as 2,3-dimercaptosuccinic acid (DMSA), is an orally administered watersoluble derivative of BAL. DMSA is available in 100 mg capsules. The
recommended regimen of DMSA is 10 mg/kg orally every 8 hr for 5 days. The DMSA–heavy metal complex is excreted in the urine and bile. A period of 2 wk between courses of chelation is recommended. Mild adverse effects include nausea, vomiting, diarrhea, loss of appetite, and transient elevations in liver enzyme levels. DMSA also may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient patients. Patients with ingestion of elemental mercury require no follow-up unless there is an underlying disease that decreases the gastrointestinal transit time. Serial abdominal radiographs to document the progression of the metal are recommended. Acute inhalation of mercury fumes and ingestion of inorganic mercury require hospitalization to monitor the respiratory and gastrointestinal status, respectively. Therapeutic abortion may be considered in pregnant patients, because of the teratogenic effect of mercury.

*Bibliography is available at Expert Consult.*
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Chapter 721  ♦  Lead Poisoning  3431

Lead Poisoning
Morri Markowitz

Lead is a metal that exists in 4 isotopic forms. Clinically, it is purely a toxicant; no organism has an essential function that is lead dependent. Chemically, its low melting point and ability to form stable compounds have made it useful in the manufacture of hundreds of products; this commercial attractiveness has resulted in the processing of millions of tons of lead ore, leading to widespread dissemination of lead in the human environment.

The blood lead level (BLL) is the gold standard for determining health effects. However, the threshold level at which lead begins to cause biochemical, subclinical, or clinical disturbance remains to be determined. The Centers for Disease Control and Prevention (CDC), recognizing that a BLL of 10 µg/dL qualifies neither as a threshold of toxicity nor as a protective parameter of children with lead exposure, changed its standard. It no longer refers to a level of concern or toxicity but has designated 5 µg/dL as the “reference value based on the 97.5th percentile of the population BLL in children aged 1-5 years to identify children living or staying for long periods in environments that expose them to lead hazards.” As a measure of the distribution of BLLs in young children, this number will change in a manner dependent on the epidemiology of BLLs rather than on identification of the starting point for toxicity.

Although stated as a reference value, it is likely that clinicians and departments of health will consider this a threshold for action. It is important to recognize that lead toxicity occurs at levels below 5 µg/dL; no safe level has been identified. In part, this reflects the accuracy limitations of available clinical laboratory methodologies.

PUBLIC HEALTH HISTORY

In the late 1970s, nearly all preschool-age children in the United States had BLLs above the current reference value of 5 µg/dL. Around that time government regulations were issued that resulted in the significant reduction of 3 main contributors to lead exposure by means of (1) the elimination of the use of tetraethyl lead as a gasoline additive, (2) the banning of lead-containing solder to seal cans of food and beverages, and (3) the application of a federal rule that limited the amount of lead allowed in paint intended for household use to less than 0.06% by weight (further reduced by the Consumer Product Safety Commission to 0.009% in 2008). Surveillance by many of the states in the United States and by national health surveys conducted by the CDC has shown that the prevalence of elevated BLLs has declined markedly. Approximately 535,000 young children currently have BLLs ≥5 µg/dL. Including all children <18 yr of age yields an estimated 705,000 with levels above the reference value (National Health and Nutritional Examination Surveys show that for 2007-2010, 0.95% of children < age 18 yr have BLL ≥5 µg/dL). Several subgroups remain at higher risk for lead poisoning. The mean BLL of non-Hispanic black children (1.8 µg/dL) is greater than that of either non-Hispanic white children (1.3 µg/dL) or Mexican American children (1.3 µg/dL); the mean BLL among poor children (1.6 µg/dL) is higher than among more well-to-do children (1.2 µg/dL). Another high-risk group that has been identified consists of recent immigrants from less-wealthy countries, including adoptees. Fortunately, children with levels high enough to be life-threatening (>100 µg/dL) are rarely seen in the United States.

As of 2014 only 6 countries continue to use leaded gasoline (Afghanistan, Algeria, Iraq, North Korea, Myanmar, and Yemen) and these are expected to phase out its use. In all countries examined, the end of this source of exposure was associated with a marked decrease in average BLLs at all ages. In Malta, after the import of red lead paint was banned and the use of lead-treated wood for fuel in bakeries was prohibited, mean BLLs of pregnant women and newborns decreased by 45%. After it was documented that children living in the neighborhood of a battery factory in Nicaragua had a mean BLL of 17.2 µg/dL whereas children in the control community had a mean BLL of 7.4 µg/dL, the factory was closed. Despite these advances, the World Health Organization estimates that nearly a quarter billion people have BLLs above 5 µg/dL; of those who are children, 90% live in developing countries, where, in some regions, BLLs may be 10-20-fold higher than in developed countries.

In 2010, the CDC and World Health Organization, after being alerted by Doctors Without Borders, identified numerous lead-contaminated villages in northern Nigeria. The grinding of ore to extract gold caused widespread lead dust dissemination. It is likely that hundreds of children died as a consequence of this activity, and all remaining children in the villages assessed to date were lead poisoned, with 97% having a BLL ≥45 µg/dL.

SOURCES OF EXPOSURE

Lead poisoning may occur in utero, because lead readily crosses the placenta from maternal blood. The spectrum of toxicity is similar to that experienced by children after birth. The source of maternal blood lead content is either redistribution from endogenous stores (i.e., the mother’s skeleton) or lead newly acquired from ongoing environmental exposure.

Several hundred products contain lead, including batteries, cable sheathing, cosmetics, mineral supplements, plastics, toys (Table 721-1),

<table>
<thead>
<tr>
<th>Table 721-1</th>
<th>Sources of Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paint chips</td>
<td></td>
</tr>
<tr>
<td>Dust</td>
<td></td>
</tr>
<tr>
<td>Soil</td>
<td></td>
</tr>
<tr>
<td>Parent’s or older child’s occupational exposure (auto repair, battery manufacturing or recycling, smelting, construction, mining, remodeling, plumbing, gun/bullet exposure, indoor firing ranges, painting)</td>
<td></td>
</tr>
<tr>
<td>Glazed ceramics</td>
<td></td>
</tr>
<tr>
<td>Herbal remedies (e.g., Ayurvedic medications)</td>
<td></td>
</tr>
<tr>
<td>Home remedies, including antiperspirants, deodorants (e.g., litargiro)</td>
<td></td>
</tr>
<tr>
<td>Jewelry (as toys or belonging to parents)</td>
<td></td>
</tr>
<tr>
<td>Stored battery casings (or living near a battery smelter)</td>
<td></td>
</tr>
<tr>
<td>Lead-based gasoline</td>
<td></td>
</tr>
<tr>
<td>Moonshine alcohol</td>
<td></td>
</tr>
<tr>
<td>Contaminated foods (e.g., Mexican candies; Ecuadorian chocolates, imported rice)</td>
<td></td>
</tr>
<tr>
<td>Indoor firing ranges</td>
<td></td>
</tr>
<tr>
<td>Imported spices (svanuri marili, saffron, kuzhambu)</td>
<td></td>
</tr>
<tr>
<td>Cosmetics (kohl, surma, kajal, tiro, lipstick)</td>
<td></td>
</tr>
<tr>
<td>Lead plumbing (water)</td>
<td></td>
</tr>
<tr>
<td>Imported foods in lead-containing cans</td>
<td></td>
</tr>
<tr>
<td>Imported toys</td>
<td></td>
</tr>
<tr>
<td>Home renovations</td>
<td></td>
</tr>
<tr>
<td>Antique toys or furniture</td>
<td></td>
</tr>
</tbody>
</table>
and traditional medicines (Table 721-2). Major sources of exposure vary among and within countries; the major source of exposure in the United States remains old lead-based paint. Approximately 38 million homes, mainly built before 1950, have lead-based paint (2000 estimate). As paint deteriorates, it chalks, flakes, and turns to dust. Improper rehabilitation work of painted surfaces (e.g., sanding) can result in dissemination of lead-containing dust throughout a home. The dust can coat all surfaces, including children’s hands. All of these forms of lead can be ingested. If heat is used to strip paint, then lead vapor concentrations in the room can reach levels sufficient to cause lead poisoning via inhalation.

**METABOLISM**

The nonnutritive hand-to-mouth activity of young children is the most common pathway for lead to enter the body. In nearly all cases, lead is ingested as a component of solids or dissolved in liquids. Cutaneous contamination with inorganic lead compounds, such as those found in pigments, does not result in a substantial amount of absorption. Organic lead compounds, such as tetraethyl lead, may penetrate through skin, however. This is rarely encountered in the United States.

The percentage of lead absorbed from the gut depends on several factors: particle size, pH, other material in the gut, and nutritional status of essential elements. Large paint chips are difficult to digest and are mainly excreted; this is fortunate as a single chip may contain a lethal dose of lead. Fine dust can be dissolved more readily, especially in an acid medium. Lead eaten on an empty stomach is better absorbed than that taken with a meal. The presence of calcium and iron may decrease lead absorption by direct competition for binding sites; iron (and probably calcium) deficiency results in enhanced lead absorption, retention, and toxicity.

After absorption, lead is disseminated throughout the body. Most retained lead accumulates in bone, where it may reside for years. It circulates bound to erythrocytes; approximately 97% in blood is bound on or in the red blood cells. The plasma fraction is too small to be measured by conventional techniques employing atomic absorption spectroscopy or anodic stripping voltammetry; it is presumably the plasma portion that may enter cells and induce toxicity. Thus, clinical laboratories report the BLL, not the serum or plasma lead level. It is possible, but not yet sufficiently shown by testing, that some of the variance in the relationship between BLLs and outcome measures of toxicity is a result of the limitations of using BLLs to assess risk. Studies that examine plasma lead concentrations in relation to its toxicity are needed.

Lead has multiple effects in cells. It binds to enzymes, particularly those with available sulfhydryl groups, changing the contour and diminishing function. For example, the heme pathway, present in all cells, consists of 8 enzymes, 3 of which are susceptible to lead inhibitory effects. The accumulation of excess amounts of heme precursors also is toxic (see Chapter 91). The last enzyme in this pathway, ferrochelatase, enables protoporphyrin to chelate iron, thus forming heme. Heme is essential for multiple metabolic pathways and not merely as a component of hemoglobin. Erythrocyte protoporphyrin levels higher than 35 µg/dL are abnormal and are consistent with lead poisoning, iron deficiency, or recent inflammatory disease.

Erythrocyte protoporphyrin levels begin to rise several weeks after BLLs have reached 20 µg/dL in a susceptible portion of the population, and are elevated in nearly all children with BLLs higher than 50 µg/dL. A drop in erythrocyte protoporphyrin levels also lags behind a decline in BLLs by several weeks, because it depends on both cell turnover and cessation of further overproduction by marrow red blood cell precursors. Measurement of the erythrocyte protoporphyrin level is, therefore, a useful tool for monitoring more severe biochemical lead toxicity.

A second mechanism of lead toxicity works via its competition with calcium. Many calcium-binding proteins have a higher affinity for lead than for calcium. Lead bound to these proteins may alter function, resulting in abnormal intracellular and intercellular signaling. Neurotransmitter release is, in part, a calcium-dependent process that is adversely affected by lead.

Although these 2 mechanisms of toxicity may be reversible, a third mechanism prevents the development of the normal tertiary brain structure. In immature mammals the normal neuronal pruning process that results in elimination of multiple intercellular brain connections is inhibited by lead. Failure to construct the appropriate tertiary brain structure during infancy and childhood may result in a permanent abnormality. A longitudinal study of childhood lead poisoning that followed a cohort from birth and into their 20s performed MRI and functional MRI–phosphorus magnetic resonance spectroscopy assessments confirmed the association of early childhood lead exposure and subsequent decreased gray and white matter volume and neuronal function. The investigators concluded that early lead exposure in life causes a persistent reorganization of brain architecture and diminished function.

**CLINICAL EFFECTS**

The BLL is the best-studied measure of the lead burden in children. Although subclinical and clinical findings correlate with BLLs in populations, there is considerable interindividual variability in this relationship. Lead encephalopathy is more likely to be observed in children with BLLs higher than 100 µg/dL; however, 1 child with a BLL of 300 µg/dL may have no symptoms, whereas another with the same level may be comatose. Susceptibility may be associated with polymorphisms in genes coding for lead-binding proteins, such as Δ-aminolevulinic acid dehydratase, an enzyme in the heme pathway.

Several subclinical effects of lead have been demonstrated in cross-sectional epidemiologic studies. Hearing and height are inversely related to BLLs in children. As BLLs increased in the study population, more sound (at all frequencies) was needed to reach the hearing threshold. Children with higher BLLs are shorter than those with lower levels; for every 10 µg increase in the BLL, the children are 1 cm shorter. Chronic lead exposure also may delay puberty. However, these associations with rising BLLs do not reach a point that would bring an individual child to medical attention.

### Table 721-2

<table>
<thead>
<tr>
<th>TRADITIONAL MEDICAL SYSTEM</th>
<th>CASES OF LEAD ENCEPHALOPATHY N (%)</th>
<th>N (%) PEDIATRIC CASES WITHIN CAM SYSTEM OR MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayurveda</td>
<td>5 (7)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Ghasard</td>
<td>1 (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Traditional Middle Eastern practices</td>
<td>66 (87)</td>
<td>66 (100)</td>
</tr>
<tr>
<td>Azarcón and greta</td>
<td>2 (3)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Traditional Chinese medicine</td>
<td>2 (3)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>76 (100)</td>
<td>72 (95)</td>
</tr>
</tbody>
</table>

CAM, complementary and alternative medicines.

Several longitudinal studies have followed cohorts of children from birth for as long as 20 yr and examined the relationship between BLLs and cognitive test scores over time. In general, there is agreement that BLLs, expressed either as levels obtained at around 2 yr of age or as a measure that integrates multiple BLLs drawn from subjects over time, are inversely related to cognitive test scores. On average, for each 1 µg/dL elevation in BLL, the cognitive score is approximately 0.25–0.50 points lower. Because the BLLs from early childhood are predictors of the cognitive test performed years later, this finding implies that the effects of lead can be permanent. Concurrent testing of lead levels and cognition sometimes also shows an inverse association.

The effect of in utero lead exposure is less clear. Scores on the Bayley Scale of Mental Development were obtained repeatedly every 6 mo for the 1st 2 yr of life in a cohort of infants born to middle-class families. Results correlated inversely with cord BLLs, a measure of in utero exposure, but not with BLLs obtained concurrently at the time of developmental testing. After 2 yr of age, all other cognitive tests performed on the cohort over the next 10 yr correlated with the BLLs at age 2 yr but not with cord BLLs, indicating that the effects of prenatal lead exposure on brain function were superseded by early childhood events and later BLLs. Later studies, performed in cohorts of Mexican children monitored from the prenatal period, confirm the association between in utero lead exposure and later cognitive outcomes. No threshold for BLL was identified in these studies; maternal BLLs between 0 and 10 µg/dL, even as early as the 1st trimester, were associated with about a 6-point drop in cognitive test scores when children were tested up to age 10 yr.

Behavior also is adversely affected by lead exposure. Hyperactivity is noted in young school-age children with histories of lead poisoning or with concurrent elevations in BLL. Older children with higher bone lead content are more likely to be aggressive and to have behaviors that are predictive of later juvenile delinquency. Multiple reports support the concept of long-term effects of early lead exposure. In 1 longitudinal study, the mothers of a cohort were enrolled during their pregnancies. BLLs were obtained early in pregnancy, at birth, and then multiple times in the offspring during the 1st 6 yr. The investigators report that the relative rate of arrests, especially for violent crimes, increased significantly in relationship to the presence of these BLLs early in life. For every 5 µg/dL increase in BLL, the adjusted arrest rate was 1.40 for prenatal BLLs and 1.27 for 6 yr BLLs. Epidemiologic data support the findings in this observational study. In an analysis that combined 2 national data sets, total annual leaded gasoline use (U.S. Geological Survey) and total reported violent criminal acts (U.S. Department of Justice), the amount of leaded gasoline used yearly was found to be strongly associated with lead poisoning rates in children with BLLs, expressed either as levels obtained at around 20–55 µg/dL, all BLLs managed over 6 mo, addressed the issue of the effects of treatment on cognitive development. Components of treatment included education regarding sources of lead and its abatement, nutritional guidance, multiple home screening may be performed on the basis of a risk assessment. Three screening young children for lead poisoning: guidance for state and local public health officials, Atlanta, 1997, Centers for Disease Control and Prevention.

**Table 721-3**

<table>
<thead>
<tr>
<th>Minimum Personal Risk Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the child live in or visit regularly a house that was built before 1950? (Include settings such as daycare, babysitter’s or relative’s home.)</td>
</tr>
<tr>
<td>2. Does the child live in or regularly visit a house built before 1978 with recent (past 6 mo) or ongoing renovations or remodeling?</td>
</tr>
<tr>
<td>3. Does the child have a sibling or playmate that has or did have lead poisoning?</td>
</tr>
</tbody>
</table>

From Screening young children for lead poisoning: guidance for state and local public health officials, Atlanta, 1997, Centers for Disease Control and Prevention.

**CLINICAL SYMPTOMS**

**Gastrointestinal Tract and Central Nervous System**

**Gastrointestinal symptoms** of lead poisoning include anorexia, abdominal pain, vomiting, and constipation, often occurring and recurring over a period of weeks. Children with BLLs higher than 20 µg/dL are twice as likely to have gastrointestinal complaints as those with lower BLLs. **Central nervous system symptoms** are related to worsening cerebral edema and increased intracranial pressure. Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death are rarely seen at levels lower than 100 µg/dL but have been reported in children with a BLL as low as 70 µg/dL. The last-reported death directly attributable to lead toxicity in the United States was in 2006 in a child with a BLL of 180 µg/dL. There is no clear cutoff BLL value for the appearance of hyperactivity, but it is more likely to be observed in children who have levels higher than 20 µg/dL.

Other organs also may be affected by lead toxicity, but symptoms usually are not apparent in children. At high levels (>100 µg/dL), renal tubular dysfunction is observed. Lead may induce a reversible Fanconi syndrome (see Chapter 529). In addition, at high BLLs, red blood cell survival is shortened, possibly contributing to a hemolytic anemia, although most cases of anemia in lead-poisoned children are a result of other factors, such as iron deficiency and hemoglobinopathies. Older patients may develop a peripheral neuropathy leading to wrist drop and footdrop.

**DIAGNOSIS**

**Screening**

It is estimated that 99% of lead-poisoned children are identified by screening procedures rather than through clinical recognition of lead-related symptoms. Until 1997 universal screening by blood lead testing of all children at ages 12 mo and 24 mo was the standard in the United States. Given the national decline in the prevalence of lead poisoning, the recommendations have been revised to target blood lead testing of high-risk populations. High risk is based on an evaluation of the likelihood of lead exposure. Departments of health are responsible for determining the local prevalence of lead poisoning, as well as the percentage of housing built before 1950, the period of peak lead paint use. When this information is available, informed screening guidelines for practitioners can be issued. For instance, in the state of New York, where a large percentage of housing was built before 1950, the Department of Health mandates that all children be tested for lead poisoning via blood analyses. In the absence of such data the practitioner should continue to test all children at both 12 mo and 24 mo. In areas where the prevalence of lead poisoning and old housing is low, targeted screening may be performed on the basis of a risk assessment. Three questions form the basis of most published questionnaires (Table 721-3), and items that are pertinent to the locale or individual may be added. If there is a lead-based industry in the child’s neighborhood, the child is a recent immigrant from a country that still permits use of lead.
gasoline, or the child has pica or developmental delay, blood lead testing would be appropriate. All Medicaid-eligible children should be screened by blood lead testing. Unfortunately, answers on questionnaires are not more successful at identifying children with lead poisoning than chance. Venous sampling is preferred to capillary sampling because the chances of false-positive and false-negative results are less than with the former.

**TREATMENT**

Once lead is in bone, it is released slowly and is difficult to remove even with chelating agents. Because the cognitive/behavioral effects of lead may be irreversible, the main effort in treating lead poisoning is to prevent it from occurring and to prevent further ingestion by already-poisoned children. The main components in the effort to eliminate lead poisoning are universally applicable to all children (and adults) and are as follows: (1) identification and elimination of environmental sources of lead exposure, (2) behavioral modification to reduce nonnutritive hand-to-mouth activity, and (3) dietary counseling to ensure sufficient intake of the essential elements calcium and iron. For the small minority of children with more-severe lead poisoning, drug treatment is available that enhances lead excretion.

During health maintenance visits a limited risk assessment is warranted, which includes questions pertaining to the most common sources of lead exposure: the condition of old paint, secondary occupational exposure via an adult living in the home, and/or proximity to an industrial source of pollution. If such a source is identified, its elimination usually requires the assistance of public health and housing agencies as well as education for the parents. The family should move out of a lead-contaminated apartment until repairs are completed. During repairs, repeated washes of surfaces and the use of high-efficiency particle accumulator vacuum cleaners help reduce exposure to lead-containing dust. Careful selection of a contractor who is certified to perform lead abatement work is necessary. Sloppy work can cause dissemination of lead-containing dust and chips throughout a home or building and result in further elevation of a child’s BLL. After the work is completed, dust wipe samples should be collected from floors and windowsills or wells to verify that the risk from lead has abated.

A single case of lead poisoning is often discovered in a household with multiple affected family members, including other young children, even in a household with a common source of exposure such as peeling lead-based paint. The mere presence of lead in an environment does not produce lead poisoning. Parental efforts at reducing the hand-to-mouth activity of the affected child are necessary to reduce the risk of lead ingestion. Handwashing effectively removes lead, but in a home with lead-containing dust, lead rapidly begins to reaccumulate on the child’s hands after washing. Therefore, handwashing is best limited to the period immediately before nutritive hand-to-mouth activity occurs.

Because there is competition between lead and essential minerals, it is reasonable to promote a healthy diet that is sufficient in calcium and iron. The recommended daily intakes of these metals vary somewhat with age. In general, for children 1 yr of age and up a calcium intake of about 1 g/day is sufficient and convenient to remember (roughly the calcium content of a quart of milk [≈1,200 mg/qt] or calcium-fortified orange juice). Calcium absorption is vitamin D dependent; milk is fortified with vitamin D, but other nutritional sources of calcium are not. A multivitamin containing vitamin D may be prescribed for children who do not drink sufficient milk or who have inadequate sunlight exposure. Iron requirements also vary with age, ranging from 6 mg/day for infants to 12 mg/day for adolescents. For children identified biochemically as being iron deficient, therapeutic iron at a daily dose of 5-6 mg/kg for 3 mo is appropriate. Iron absorption is enhanced when iron is ingested with ascorbic acid (citrus juices). Giving additional calcium or iron above the recommended daily intakes to mineral-sufficient children has not been shown to be of therapeutic benefit in the treatment of lead poisoning.

**Drug treatment** to remove lead is lifesaving for children with lead encephalopathy. In nonencephalopathic children, it prevents symptom progression and further toxicity. Guidelines for chelation are based on the BLL. A child with a venous BLL of 45 µg/dL or higher should be treated. Four drugs are available in the United States: 2,3-dimercaptosuccinic acid (DMSA [succimer]), CaNa₂EDTA (versenate), British antilewisite (BAL [dimercaprol]), and penicillamine. DMSA and penicillamine can be given orally, whereas CaNa₂EDTA and BAL can be administered only parenterally. The choice of agent is guided by the severity of the lead poisoning, the effectiveness of the drug, and the ease of administration (Table 721-4). Children with BLLs of 44-70 µg/dL may be treated with a single drug, preferably DMSA. Those with BLLs of 70 µg/dL or greater require 2-drug treatment: CaNa₂EDTA in combination with either DMSA or BAL for those without evidence of encephalopathy, or CaNa₂EDTA and BAL for those with encephalopathy. Published data on the combined treatment with CaNa₂EDTA and DMSA for children with BLLs higher than 100 µg/dL are very limited. However, anecdotal information derived from the treatment of hundreds of severely lead poisoned children in northern Nigeria indicates that single-drug treatment with DMSA is lifesaving, although the degree of residual damage in survivors has not been reported.

Acute drug-related toxicities are minor and reversible. These include gastrointestinal distress, transient elevations in transaminases, active urinary sediment, and neutropenia. These types of events are least common for CaNa₂EDTA and DMSA and more common for BAL and

<table>
<thead>
<tr>
<th>NAME</th>
<th>SYNONYM</th>
<th>DOSE</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succimer</td>
<td>Chemet, 2,3-dimercaptosuccinic acid (DMSA)</td>
<td>350 mg/m² body surface area/dose (not 10 mg/kg) q8h, PO for 5 days, then q12h for 14 days</td>
<td>Gastrointestinal distress, rashes; elevated LFTs, depressed white blood cell count</td>
</tr>
<tr>
<td>Edetate*</td>
<td>CaNa₂EDTA (calcium disodium edetate), versenate</td>
<td>1,000-1,500 mg/m² body surface area/day; IV infusion—continuous or intermittent; IM divided q6h or q12h for 5 days</td>
<td>Proteinuria, pyuria, rising blood urea nitrogen/creatinine—all rare</td>
</tr>
<tr>
<td>British antilewisite (BAL)</td>
<td>Dimercaprol</td>
<td>300-500 mg/m² body surface area/day; IM only divided q4h for 3-5 days. Only for BLL ≥70 µg/dL</td>
<td>Gastrointestinal distress, altered mentation; elevated LFTs, hemolysis if glucose-6-phosphate dehydrogenase deficiency; no concomitant iron treatment</td>
</tr>
<tr>
<td>D-Pen</td>
<td>Penicillamine</td>
<td>10 mg/kg/day for 2 wk increasing to 25-40 mg/kg/day; oral, divided q12h. For 12-20 wk</td>
<td>Rashes, fever; blood dyscrasias, elevated LFTs, proteinuria Allergic cross reactivity with penicillin</td>
</tr>
</tbody>
</table>

*Always given as the calcium salt; never as the sodium salt without calcium.

BLL, blood lead level; IM, intramuscularly; IV, intravenously; LFT, liver function test; PO, by mouth.

penicillamine. All of the drugs are effective in reducing BLLs when given in sufficient doses and for the prescribed time. These drugs also may increase lead absorption from the gut and should be administered to children in lead-free environments. Some authorities also recommend the administration of a cathartic immediately prior to or concomitant with the initiation of chelation to eliminate any lead already in the gut.

None of these agents removes all lead from the body. Within days to weeks after completion of a course of therapy the BLL rises, even in the absence of new lead ingestion. The source of this rebound in the BLL is believed to be bone. Serial examinations of bone lead content have shown that chelation with CaNa$_2$EDTA is associated with a decline in bone lead levels but that residual bone lead remains detectable even after multiple courses of treatment.

Repeat chelation is indicated if the BLL rebounds to 45 µg/dL or higher. Children with initial BLLs higher than 70 µg/dL are likely to require more than 1 course. A minimum of 3 days between courses is recommended to prevent treatment-related toxicities, especially in the kidney.

The indication for chelation therapy for children with BLLs <45 µg/dL is less clear. Although use of these drugs in children with BLLs from 20-44 µg/dL will result in transiently lowered BLLs, and in some cases reversal of lead-induced enzyme inhibition, few such children increase their excretion of lead significantly during chelation, raising the question of whether any long-term benefit is achieved. A study of 2 yr old children with BLLs of 20-44 µg/dL who were randomized to receive either DMSA or placebo found that the drop in BLLs was greater in the 1st 6 mo after enrollment in the DMSA-treated group, but the levels converged by 1 yr of follow-up. Mean cognitive test scores obtained at 4 and 7 yr of age were not statistically different between the groups. Chelation with DMSA (and CaNa$_2$EDTA) is not recommended for all children with BLLs <45 µg/dL. It remains to be demonstrated whether other chelating agents available in the United States or elsewhere are effective at either substantially reducing body stores (bone) of lead or at reversing the cognitive deficits attributable to lead at these BLLs.

With successful intervention (with or without chelation), BLLs decline, with the greatest fall in BLL occurring in the 1st 2 mo after therapy is initiated. Subsequently, the rate of change in BLL declines slowly so that by 6-12 mo after identification, the BLL of the average child with moderate lead poisoning (BLL >20 µg/dL) will be 50% lower. Children with more markedly elevated BLLs may take years to reach the CDC reference level, 5 µg/dL, even if all sources of lead exposure have been eliminated, behavior has been modified, and nutrition has been maximized. Early screening remains the best way of avoiding and therefore obviating the need for the treatment of lead poisoning.

Bibliography is available at Expert Consult.
Chapter 721  Lead Poisoning  3435.e1

Bibliography
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Mielke HW, Zahran S: The urban rise and fall of air lead (Pb) and the latent surge and retreat of societal violence, Environ Int 43:48–55, 2012.
The clinical syndromes produced by mushroom poisoning are divided according to the rapidity of onset of symptoms and the predominant system involved (Table 722-1). The symptoms are caused by the principal toxin present in the ingested mushrooms. The 8 major toxins produced by mushrooms are categorized as cyclopeptides, monomethylhydrazine, muscarine, hallucinogenic indoles, isoxazole, coprine (disulfiram-like reaction), orellanine, and gastrointestinal tract-specific irritants. The edible wild mushroom *Tricholoma equestre* is associated with delayed rhabdomyolysis, and *Clitocybe amoenolens* and *Clitocybe acromelalga* have been reported to cause erythromelalgia. The toxins responsible for these effects are unknown. An enzyme-linked immunosorbent assay immunoassay is available to detect amanitotoxin; additional rapid tests are becoming available to identify other specific toxins.

Symptoms after eating mushrooms may not be the direct effect of a toxin but may be an allergic reaction or a toxic effect of pesticides or other contaminants. In addition, all who ate the same mushroom may not become sick or if they do they may become sick at different intervals. Table 722-2 lists general principles of management.

**GASTROINTESTINAL: DELAYED ONSET**

**Amanita Poisoning**

Poisonings by species of *Amanita* and *Galerina* account for 95% of the fatalities from mushroom intoxication; the mortality rate for this group is 5-10%. Most species produce 2 classes of cyclopeptide toxins: (1) phallotoxins, which are heptapeptides believed to be responsible for the early symptoms of *Amanita* poisoning, and (2) amanitotoxin, an octapeptide that inhibits nuclear RNA polymerase II and subsequent production of messenger RNA leading to impaired protein synthesis and cell death. Cells with high turnover rates, such as those in the gastrointestinal mucosa, kidneys, and liver, are the most severely affected. Other suggested toxin effects are induction of apoptosis, glutathione depletion in the liver, and oxygen free radical formation. Acute yellow atrophy of the liver and necrosis of the proximal renal tubules are found in lethal cases.

The clinical course of poisoning with *Amanita* or *Galerina* species is biphasic. Nausea, vomiting, and severe abdominal pain ensue 6-24 hr after ingestion. Profuse watery diarrhea follows shortly thereafter and may last for 12-24 hr or longer. During this time, patients become severely dehydrated. From 24-48 hr after poisoning, jaundice, hypertransaminasemia (peaking at 72-96 hr), renal failure, and coma occur. Death occurs 4-7 days after the ingestion. A prothrombin time less than 10% of control is a poor prognostic factor.

**Treatment**

Treatment for *Amanita* poisoning is both supportive and specific. Fluid loss from severe diarrhea during the early course of the illness is profound, requiring aggressive correction of fluid loss, electrolytes, and acid-base disturbances. In the late phase of the disease, management of renal and hepatic failure is also necessary.

Specific therapy for *Amanita* poisoning is designed to remove the toxin rapidly and to block binding at its target site. Oral activated charcoal is recommended as part of the initial treatment for children with *Amanita* poisoning. Forced diuresis should be avoided, as this increases renal exposure. For significant ingestions, consider silibinin (5 mg/kg IV over 1 hr followed by a continuous intravenous infusion of 20 mg/kg/24 hr) for 3 days postingestion. If silibinin is not available, intravenous penicillin G (400,000 units/kg/24 hr) may be used. Silibinin and penicillin G inhibit binding of both toxins, interrupt enterohepatic recirculation of amanitotoxin, and protect the liver from further injury. Acetylcysteine has shown promise in some studies. Hemodialysis and hemoperfusion are also recommended as part of the initial treatment for intoxicated children. Orthotopic liver transplantation is recommended for children with severe hepatic failure.

**Monomethylhydrazine Intoxication**

Species of *Gyromitra* contain gyromitrin which decomposes in the stomach to form monomethylhydrazine (CH₃NHNH₂) and inhibits
Central nervous system (CNS) enzymatic production of γ-aminobutyric acid. Monomethylhydrazine also oxidizes iron in hemoglobin, resulting in hemoglobinuria. Children with Gyromitra poisoning experience vomiting, diarrhea, hematochezia, and abdominal pain within 6-24 hr of ingestion of the toxin. CNS symptoms such as vertigo, diplopia, headache, ataxia, and seizures develop later in the clinical course. Hemolysis and methemoglobinemia (see Chapter 462.6) are rare but potential life-threatening complications of gyromitrin poisoning.

**Treatment**

Hypovolemia from gastrointestinal fluid losses and seizures require supportive intervention. Pyridoxal phosphate, the coenzyme that catalyzes the production of γ-aminobutyric acid, can reverse the effects of monomethylhydrazine when administered in high doses. Pyridoxine hydrochloride (25 mg/kg infused over 30 min) is given at a frequency that is dependent on clinical improvement. Diazepam is given for persistent seizures. Parenteral administration of methylene blue is indicated if the methemoglobin concentration exceeds 30%; severe methemoglobinemia may require dialysis. Blood transfusions may be required for significant hemolysis.

**RENA: DELAYED ONSET**

**Orellanine Poisoning**

Species of Cortinarius contain the heat-stable toxin bipyridyl orellanine, which causes severe nonglomerular renal injury characterized by
interstitial fibrosis and acute tubular necrosis. Although the exact mechanism of injury is not fully understood, a metabolite of orellanine is thought to inhibit renal protein synthesis. Cortinarius poisoning is characterized by nausea, vomiting, and diarrhea that manifest 36-48 hr after ingestion. Although the initial symptoms may be trivial, more serious renal toxicity occurs in several days. Acute renal failure occurs in 30-50% of those affected, beginning with polyuria and progressing to renal failure (see Chapter 535).

**Treatment**

Treatment for orellanine poisoning is supportive. Early presentation, within 4-6 hr after ingestion, can be treated with activated charcoal and gastric lavage. Hemodialysis may be needed in patients suffering from renal failure. Most patients recover within 1 mo but chronic renal insufficiency develops in one third to one half of patients who subsequently require renal transplantation.

**AUTONOMIC NERVOUS SYSTEM: RAPID ONSET**

**Muscarine Poisoning**

Mushrooms of the genera *Inocybe* and, to a lesser degree, *Clitocybe* contain muscarine or muscarine-related compounds. These quaternary ammonium derivatives bind to postsynaptic receptors, producing an exaggerated cholinergic response.

The onset of symptoms is rapid (30 min to 2 hr after consumption) and intoxication is characterized by a hypercholinergic response: diaphoresis, excessive lacrimation, salivation, miosis, bradycardia, hypotension, urinary and fecal incontinence, and vomiting. Respiratory distress caused by bronchospasm and increased bronchopulmonary secretions is the most serious complication. The symptoms subside spontaneously within 6-24 hr.

**Treatment**

Atropine sulfate, the specific antidote, is administered intravenously (0.01 mg/kg; maximum: 2 mg). This is repeated until the pulmonary symptoms resolve or the patient becomes overtly tachycardic.

**Coprine Ingestion**

*Coprinus atramentarius* and *Clitocybe clavipes* contain coprine. Like disulfiram (Antabuse; Odyssey Pharmaceuticals, Inc.), coprine inhibits the metabolism of acetaldehyde after ethanol ingestion. The clinical manifestations result from accumulation of acetaldehyde.

Coprine intoxication becomes apparent after ethanol ingestion and may occur up to 5 days after consumption of the mushroom. Hyperemia of the face and trunk, tingling of the hands, metallic taste, tachycardia, and vomiting occur acutely. Hypotension may result from intense peripheral vasodilation. The syndrome typically is self-limited and lasts only several hours. No specific antidote is available. If hypotension is severe, vascular reexpansion with isotonic parenteral solutions may be required. Small oral doses of propranolol have also been suggested.

**CENTRAL NERVOUS SYSTEM: RAPID ONSET**

**Isolexazole Intoxication**

Although *Amanita muscaria* and *Amanita pantherina* may contain muscarine, the toxins responsible for the CNS symptoms after ingestion of these mushrooms are muscimol and ibotenic acid, the heat-stable derivatives of the isoxazoles. Muscimol, a hallucinogen, and ibotenic acid, an insecticide, act as γ-aminobutyric acid agonists. From 30 min to 3 hr after ingestion, CNS symptoms appear: obtundation, alternating lethargy and agitation, and, occasionally, seizures. Nausea and vomiting are uncommon. If large amounts of muscarine are contained in the mushroom, symptoms of cholinergic crisis also may occur.

Specific therapy must be carefully selected. If an exaggerated cholinergic response is observed, atropine should be administered. Because ingestions of *A. muscaria* often are associated with anticholinergic findings, the acetylcholinesterase inhibitor physostigmine is often used to reverse the delirium and coma. Benzodiazepines also are used for the agitation and delirium. Seizures can be controlled with diazepam. In most cases, however, early treatment with ipecac (if the patient is conscious) and close observation are all that is required.

**Indole Intoxication**

Mushrooms belonging to the genus *Psilocybe* ("magic mushrooms") contain psilocybin and psilocin, 2 psychotropic compounds. Within 30 min after ingestion, patients experience euphoria and hallucinations, often accompanied by tachycardia and mydriasis. Fever and seizures have also been observed in children with psilocybin poisoning. These symptoms are short lived, usually lasting for 6 hr after consumption of the mushroom. Treatment consists of rest and observation in a quiet environment. Severely agitated patients may show response to diazepam.

**GASTROINTESTINAL: RAPID ONSET**

Many mushrooms from various genera produce local gastrointestinal manifestations. The causative toxins are diverse and largely unknown. Within 1 hr of ingestion, patients experience acute abdominal pain, nausea, vomiting, and diarrhea. Symptoms may last from hours to days, depending on the species of mushroom.

**Treatment** is mainly supportive. Children with large fluid losses may require parenteral fluid therapy. It is imperative to differentiate ingestion of mushrooms of this class from ingestion of *Amanita* and *Galerina* species containing cyclopeptide toxins.

*Bibliography is available at Expert Consult.*

**722.2 Solanine Poisoning**

**Denise A. Salerno and Stephen C. Aronoff**

Potatoes exposed to light and allowed to turn green and/or sprout produce a number of alkaloid glycosides containing the cholesterol derivative solanidine. Two of these glycosides, α-solanine and α-chaconine, are found in highest concentration in the peels of greened potatoes and in the sprouts. Some solanine can be removed by boiling but not by baking. The major effect of α-solanine and α-chaconine is the reversible inhibition of cholinesterase. Cardiototoxic and teratogenic effects have also been reported.

**Clinical manifestations** of solanine and chaconine poisoning intoxication occur within 7-19 hr after ingestion. The most common symptoms are vomiting, abdominal pain, and diarrhea; in more severe instances of poisoning, neurologic symptoms, including drowsiness, apathy, confusion, weakness, and vision disturbances, are rarely followed by coma or death.

**Treatment** of solanine poisoning is largely supportive. In the most severe cases, symptoms resolve within 11 days.

*Bibliography is available at Expert Consult.*

**722.3 Seafood Poisoning**

**Denise A. Salerno and Stephen C. Aronoff**

Ciguatera fish poisoning, has been reported in Florida, Hawaii, French Polynesia, the Marshall Islands, Caribbean and South Pacific islands, and the Virgin Islands. With modern methods of transportation, the illness now occurs worldwide. Gruper is the most commonly identified source of the toxin, followed by snapper, kingfish, amberjack, dolphin, eel, and barracuda. Poisoning has also been associated with farm-raised salmon. The dinoflagellate *Gambierdiscus toxicus*, a microscopic unicellular organism found along coral reefs, produces high concentrations of ciguatoxin and maitotoxin. The toxins are passed along the food chain.
Bibliography
Bibliography


from small herbivorous fish that consume the dinoflagellate to larger predatory fish and then to humans. These toxins are harmless in fish but produce distinct clinical symptoms in humans.

The lipid ciguatoxin-1 is odorless, colorless, and tasteless and is not destroyed by cooking or freezing. Ciguatoxin-1 increases the sodium ion permeability of excitable membranes and depolarizes nerve cells, actions that are inhibited by calcium and tetrodotoxin.

Between 2 and 30 hr after ingestion, ciguatoxin poisoning typically produces a biphasic illness. The initial symptoms are not specific and are of gastrointestinal origin (diarrhea, vomiting, nausea, and abdominal pain). The second phase occurs within a few days of ingestion and consists of intense itching, anxiety, myalgias, painful intercourse, and rash on palms and soles; the neurologic symptoms of circumoral or extremity dysesthesias (characterized by reversal of hot and cold sensation) are characteristic of this disease and may last for months. Tachycardia, bradycardia, hypotension, and death occur infrequently. Eating fish organs, roe, or viscera is associated with greater symptom severity. The diagnosis of ciguatera fish poisoning is based on clinical presentation and a compatible epidemiologic history; the diagnosis is confirmed by testing the ingested fish for toxin. There is no human biomarker to confirm ciguatera fish poisoning.

Treatment
Treatment of ciguatera fish poisoning is supportive. Gastric lavage is recommended to remove any remaining toxin. Intravenous fluids may be required for severe diarrhea, and parenteral administration of calcium can be used to treat hypotension. Once adequate hydration is established, mannitol (0.5-1.0 g/kg, IV over 30-45 min) given within 48-72 hr of the toxic fish ingestion is recommended for reduction of acute symptoms (especially neurologic symptoms) and possible prevention of chronic neurologic symptoms. Various other medications and herbal remedies have been tried, with variable results. Most cases are self-limited, and death occurs in less than 0.1% of cases.

SCOMBROID (PSEUDOALLERGIC) FISH POISONING
Ingestion of members of the Scomberesocidae and Scombridae families, including albacore, mackerel, tuna, bonita, and kingfish, have been linked to major outbreaks of pseudoallergy fish poisoning. Noncombroid fish and marine mammals, such as mahi-mahi (dolphin fish), swordfish, and bluefish, also are associated with poisoning.
Scembrotoxin, either histamine or the product of the action of the toxin on fish flesh, is responsible for the clinical syndrome. Histidine is found in high concentrations in the flesh of scombroid fish; the action of bacterial decarboxylases during putrification converts the histidine to histamine. Fish containing more than 20 mg of histamine per 100 g of flesh are toxic. In patients receiving isomiazid, a potent histaminase blocker, ingestion of fish flesh containing a lower concentration of histamine may be toxic.

The onset of clinical manifestations is acute and occurs within 10 min to 2 hr of ingestion. The most common symptoms and signs are diarrhea, erythema, sweating, flushing, diaphoresis, urticaria, nausea, and headache (Fig. 722-1). Abdominal pain, tachycardia, oral burning or numbness, dizziness, respiratory distress, hives, and facial swelling also occur. The illness is usually self-limited, terminating within 8-24 hr.

Treatment
Treatment is mainly supportive. Gastric lavage decreases continued absorption of histamine. With severe diarrhea, fluid replacement may be necessary. Antihistamines have been variably successful. Four patients with severe toxicity treated with cimetidine (a histamine blocker) showed rapid response. Because data on these possible treatments are limited, cimetidine or ranitidine should be reserved for severe cases.

PARALYTIC SHELLFISH POISONING
Mussels, clams, oysters, scallops, and other filter-feeding mollusks may become contaminated during dinoflagellate blooms or “red tides.” During periods of contamination, water in coastal areas can be colored red by the algae; this sign is the origin of the term red tide. (Such discoloration does not necessarily indicate the presence of toxin, and toxin may be present in high quantities without discoloration. Nonetheless, discolored water should be regarded with suspicion.) The dinoflagellates Alexandrium spp. and Gymnodinium catenatum often are responsible for these red tides and contain several potent neurotoxins. Paralytic shellfish poisoning is a distinctive neurologic illness caused by 20 closely related heat-stable paralytic shellfish toxins. Saxitoxin is the most potent of the neurotoxins responsible for paralytic shellfish poisoning. This toxin prevents nerve conduction by inhibiting the sodium–potassium pump. Other toxins may be bioconverted to less toxic compounds. Consumption of bivalves, such as mussels, scallops, and clams, is the usual pathway of intoxication, although crustaceans and fish have been implicated as well.

The onset of clinical manifestations of paralytic shellfish poisoning occurs rapidly, 30 min to 2 hr after ingestion. Abdominal pain and
nausea are common. Paresthesias are common and occur circumorally or in a stocking-glove distribution, or both. Perioral numbness or tingling, diplopia, ataxia, dysarthria, and the sensation of floating are seen less commonly. Hot-cold reversal in temperature sensation is not unusual. In severe cases, respiratory failure from diaphragmatic paralysis may result. Swimming in the water during a red tide episode does not appear to have neurologic sequelae, although skin or mucosal irritation may result.

**Treatment**

No antidote for paralytic shellfish poisoning is known. Supportive care, including mechanical ventilation, may be needed. Although the symptoms are usually self-limited and short-lived, weakness and malaise may persist for weeks after ingestion.

**NEUROTOXIC SHELLFISH POISONING**

Neurotoxic shellfish poisoning is a rare disease caused by molluscan shellfish contaminated with brevetoxins. Shellfish harvested along the Gulf of Mexico during or right after a red tide are at risk of contamination with brevetoxins produced by the dinoflagellate *Karenia brevis*. There has also been recent evidence of brevetoxin production by raphidophytes (*Chattonella* spp.). Brevetoxins are a group of more than 10 lipid-soluble neurotoxins that activate sodium ion channels, causing nerve membrane depolarization. Shellfish are not affected by the brevetoxins. Rinsing, cleaning, cooking, and freezing do not destroy the toxins. Consumption of contaminated shellfish goes unnoticed because the brevetoxins cannot be detected by taste or smell.

The onset of clinical manifestations of neurotoxic shellfish poisoning occurs from within a few min up to 18 hr after consumption. The majority of symptoms are gastrointestinal (nausea, vomiting, and diarrhea) or neurologic (numbness and tingling of the face, mouth, extremities, ataxia, partial limb paralysis, reversal of hot and cold sensation, slurred speech, headache, and fatigue). Neurotoxic shellfish poisoning is similar to a mild case of paralytic shellfish poisoning.

**Treatment**

There are no specific antidotes for brevetoxins. Treatment involves mostly supportive care. Brevenal, a natural antagonist of brevetoxin produced by *K. brevis*, may be used as a form of treatment in the future.

**DIARRHETIC SHELLFISH POISONING**

Several outbreaks of diarrhetic shellfish poisoning have been reported in Europe after consumption of mussels, cockles, and other shellfish. The dinoflagellates *Dinophysis* and *Prorocentrum* produce okadaic acid and its derivatives, the dinophysistoxins. These compounds inhibit protein phosphatases. The intracellular accumulation of phosphorylated proteins causes increased fluid secretion by gut cells via calcium influx, which is mediated by cyclic adenosine monophosphate and prostaglandins.

Patients have severe diarrhea. Care is supportive and directed at rehydration. The illness is self-limited, and recovery occurs in 3-4 days; few patients require hospitalization.

**AMNESIC SHELLFISH POISONING**

Amnesic shellfish poisoning was first reported in 1987 in Canada when a group of people demonstrated severe gastroenteritis as well as neurologic symptoms, including memory loss, after eating mussels from Prince Edward Island. Subsequent cases have been identified after consumption of shellfish from the United States, Spain, and the United Kingdom. The responsible toxin, domoic acid, comes from a diatom, *Pseudonitzschia multiseries*, and is a potent glutamate agonist, disrupting neurochemical transmission in the brain. It also binds to glutamate receptors, which increase calcium influx, producing neuronal swelling in the hippocampal area of the brain and death.

The initial clinical manifestations are gastrointestinal. Memory loss is closely related to advanced age. Those patients <40 yr are more likely to suffer only from diarrhea, whereas those >50 yr suffer from short-term memory loss lasting months to years.

**AZASPIRACID POISONING**

The azaspiracids are a class of algal toxins. Azaspiracid poisoning results from ingestion of contaminated bivalve shellfish, especially mussels. Azaspiracids are distributed throughout the muscle tissue in the shellfish. Azaspiracid is cytotoxic to cells and an inhibitor of Ca<sup>2+</sup> channels in plasma membranes. Symptoms start 6-18 hr after ingestion and include nausea, vomiting, severe stomach cramps, and diarrhea, which often persist up to 5 days.

**Bibliography is available at Expert Consult.**

**722.4 Melamine Poisoning**

Denise A. Salerno and Stephen C. Aronoff

Melamine (1,3,5-triazine-2,4,6-triamine, or C<sub>3</sub>H<sub>6</sub>N<sub>6</sub>), a compound developed in the 1830s, is found in many plastics, adhesives, laminated products, cement, cleansers, fire retardant paint, and more. Melamine poisoning from food products was unheard of until 2007, when melamine-tainted pet food caused the death of many dogs and cats in the United States. In 2008, feeding of melamine-tainted infant formula to more than 300,000 children resulted in kidney injuries, 50,000 hospitalizations, and 6 deaths in China. This was the first reported epidemic of melamine-tainted milk products.

Melamine contains 66% nitrogen by mass. The illegal addition of melamine to infant formula can give the formula a milky appearance and falsely raise the protein content as measured by nitrogen testing. Melamine, combined with cyanuric acid, forms cyanurate crystals in the kidneys. Along with protein, uric acid, and phosphate, melamine forms renal calculi.

Clinical manifestations are initially subtle and nonspecific. The severity is dose related. The first symptoms in affected infants are unexplained crying (especially when urinating), vomiting, and discolored urine caused by the formation of stones and gravel in the urinary tract. Urinary obstruction and acute renal failure follow. In the absence of a specific diagnosis, death from renal failure occurs. Whether children with melamine-induced renal failure will have chronic sequelae is currently unknown. Animal studies have shown that melamine may cause cognitive impairment but further investigation is needed.

The melamine stones and gravel can be treated with hydration, alkalinization, or lithotripsy. Acute renal failure requires supportive care and dialysis if needed.

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**Bibliography**

**Ciguatera Fish Poisoning**


**Scombroid Fish Poisoning**


**Shellfish Poisoning**


**Fish Poisoning**


Bibliography

Tragically, increasing numbers of children are being victimized by terrorist actions. Brought to the forefront of American consciousness by Timothy McVeigh’s references to child fatalities as “collateral damage” during the Oklahoma City bombing in April 1995, the intentional targeting of children became firmly ensconced as a global reality with the attack upon a school in Beslan, Russia, in September 2004. The attack, which left 334 (including 186 children) dead, presaged additional attacks specifically directed against children at an Amish School in Pennsylvania in 2006, at a camp for teenagers in Utoya, Norway, in
2011, and at Sandy Hook Elementary School in Connecticut in 2012, among others.

Paralleling the targeting of children is an apparent trend toward the use of “unconventional” weapons of terror. In 1984, members of the Rajneeshee cult employed *Salmonella typhi* in a wave of intentional poisonings that affected 751 persons, including 142 teenage patrons of a popular pizza parlor. In 1995, the Aum Shinrikyo cult killed 12 and sickened thousands by intentionally releasing sarin nerve agent in the Tokyo subway system. A disgruntled scientist deployed anthrax spores via the U.S. mail in October 2001, killing 5 and injuring 17 in an attack upon a nation already reeling in the wake of the 9/11 attacks.

These developments remind us that terrorists can strike at any time utilizing any number of unconventional weapons, including biologic and chemical agents. Children will not be spared in these attacks on civilians, and, indeed, schools and daycare sites may be the targets of these actions.

**ETIOLOGY**

Terrorists may choose to use weapons of opportunity, agents that for some reason are readily available to some member of the terrorist group. The motives of terrorists often are obscure and difficult to predict. Prevention and response strategies should thus concentrate not on those agents most likely to be used but, rather, on those agents that, if used, would constitute the gravest potential threats to public health and security.

Biologic threat agents, including pathogens and toxins, have been divided by the Centers for Disease Control and Prevention into 3 categories, with category A including diseases caused by those 6 agents posing the greatest threat: anthrax, plague (see Chapter 203.3), tularemia (see Chapter 206), smallpox, botulism (see Chapter 210), and the viral hemorrhagic fevers (see Chapter 271). Terrorists could also procure and release a vast array of potentially harmful chemicals. Tank cars full of flammable industrial gases and liquids, corrosive industrial acids and bases, poisonous compounds such as cyanides and nitrates, pesticides, dioxins, and explosives traverse our railways and roads daily. Four classes of “military-grade” chemicals with a history of use in warfare or manufactured specifically for use as weapons include the organophosphate-based nerve agents, vesicants, “blood agents” (cyanides), and certain pulmonary irritants or “choking agents.”

**EPIDEMIOLOGY AND PEDIATRIC-SPECIFIC CONCERNS**

Large-scale attacks on civilian targets will likely involve pediatric victims, and children may be more susceptible than adults to the effects of certain biologic and chemical agents (see Chapter 719). A thinner and less-keratinized epidermis makes dermally active chemical agents, such as mustard, a greater risk to children than adults. A larger surface area per unit volume further increases the problem. A small relative blood volume makes children more susceptible to the volume losses associated with enteric infections such as cholera and to gastrointestinal intoxications such as might be seen with exposure to the staphylococcal enterotoxins. Children’s high minute ventilation, compared with that of adults, increases the threat of agents delivered via the inhalational route. The fact that children live “closer to the ground” compounds this effect when heavier-than-air chemicals are involved. An immature blood–brain barrier may heighten the risk of central nervous system toxicity from nerve agents. Developmental considerations make it less likely that a child would readily flee an area of danger, thereby increasing exposure to these various adverse effects.

Children appear to have a unique susceptibility to certain potential agents that might be used by terrorists. Although adults generally suffer only a brief, self-limited incapacitating illness after infection with *Venezuelan equine encephalitis* virus, young children are more likely to experience seizures, permanent neurologic sequelae, and death. In the case of smallpox, waning herd immunity may disproportionately affect that children. Vaccine-induced immunity to smallpox probably diminishes significantly after ages 3–10 yr. Although most adults are considered susceptible to smallpox, given that routine civilian immunization ceased in the early 1970s, older adults may have some residual protection from death, if not from the development of disease. Today’s children are among the first to grow up in a world without any individual or herd immunity to smallpox.

Children also may experience unique disease manifestations not seen in adults; suppurative parotitis is a common characteristic ring among children with melioidosis but is not generally seen in adults with *Burkholderia pseudomallei* infection (see Chapter 205.2).

Pediatricians are likely to experience unique problems in managing childhood victims of biologic or chemical attack. Many of the drugs useful in treating such casualties are unfamiliar to pediatricians or have relative contraindications in childhood. The fluoroquinolones and tetracyclines are commonly cited as agents of choice in the treatment and prophylaxis of anthrax, plague, tularemia, brucellosis, and Q fever. Both drug classes are often avoided in children, although the risk of morbidity and mortality from diseases induced by agents of bioterrorism far outweighs the minor risks associated with short-term use of these agents. Ciprofloxacin received, as its first licensed pediatric indication, FDA approval for use in the prophylaxis of anthrax after inhalational exposure during a terrorist attack. Doxycycline and levofloxacin are licensed specifically in children for the same indication and levofloxacin is also licensed for postexposure prophylaxis of children against plague. Immunizations potentially useful in preventing biologic agent–induced diseases are often not approved for use in pediatric patients. The available anthrax vaccine is licensed only for those between 18 and 65 yr of age. The plague vaccine, currently out of production and probably ineffective against inhalational exposures, was approved only for individuals ages 18–61 yr. The smallpox vaccine, a live vaccine employing vaccinia virus, can cause fatal vaccinia and dermohypodermitis when given to pregnant women.

Many otherwise useful pharmaceutical agents are not available in pediatric dosing regimens. The military distributes nerve agent antidote kits consisting of prefilled autoinjectors designed for the rapid administration of atropine and pralidoxime. Many emergency departments and some ambulances stock these kits. The doses of agents contained in the nerve agent antidote kit are calculated for soldiers and thus are far in excess of those appropriate for young children, and pediatric pralidoxime autoinjectors are not yet available. Atropine autoinjectors specifically formulated for children are approved by the FDA and are available.

Although physical protective measures and devices (e.g., “gas masks”) are likely to be of little utility in a civilian terrorism setting, such commercially available devices are not often available in pediatric sizes. The Israeli experience during the first Gulf War suggests that frightened parents may improperly use such masks on their children, resulting in inadvertent suffocation.

In the event of a large-scale terrorist attack, there may be an insufficient number of pediatric hospital beds. In any large disaster, excess bed capacity might potentially be provided at civilian and veterans hospitals under the auspices of the National Disaster Medical System, but that system makes no specific provision for pediatric beds.

**CLINICAL MANIFESTATIONS**

Should a terrorist attack occur, clinicians may be called on to make prompt diagnoses and render rapid lifesaving treatments before the results of confirmatory diagnostic tests are available. Although each potential agent of terrorism produces its own unique clinical manifestations, it is useful to consider their effects in terms of a limited number of distinct clinical syndromes. This approach helps clinicians make prompt, rational decisions regarding empirical therapy. Casualties resulting from a terrorist attack would either experience symptoms immediately upon exposure to an agent (or within the 1st several hr after exposure) or, alternatively, would see their symptoms develop slowly over a period of days to weeks. In the former case, the sinister nature of the event is often obvious and the etiology more likely to be conventional or chemical in nature. Biologic agents differ from conventional, chemical (see Chapter 719), and nuclear (see Chapter 718) weapons in that they have inherent incubation periods. Consequently, patients are likely to present removed in time and place from the point...
Diseases Caused By Agents of Chemical and Biologic Terrorism, Classified By Syndrome

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of an unannounced and unnoticed exposure to a biologic agent. Whereas traditional first responders, such as firefighters and paramedics, may be at the forefront of a conventional or chemical terrorism response, the primary care physician is likely to constitute the first line of defense against the effects of a biologic agent.

Casualties can thus be categorized as either immediate or delayed in presentation. Within each of these categories, patients can be further classified as having primarily respiratory, neuromuscular, or dermatologic manifestations (Table 723-1). A limited number of agents may cause each particular syndrome, permitting institution of empiric therapy targeted at a short list of potential etiologies. The viral hemorrhagic fevers might manifest as fever and a bleeding diathesis; these agents are considered separately in Chapter 271. In most cases, supportive care is the mainstay of hemorrhagic fever treatment.

**Sudden-Onset Neuromuscular Syndrome: Nerve Agents**

The very rapid onset of neuromuscular symptoms after an exposure should lead the clinician to consider nerve agent intoxication. The nerve agents (tabun, sarin, soman, and VX) are organophosphate analogs of common pesticides that act as potent inhibitors of the enzyme acetylcholinesterase. They are hazardous via ingestion, inhalation, or cutaneous absorption (see Chapter 63).

The inhibition of cholinesterase by these compounds results in the accumulation of acetylcholine at neural and neuromuscular junctions, causing excess stimulation. The resultant cholinergic syndrome involves central, nicotinic, and muscarinic effects. Central effects include altered mental status progressing rapidly to lethargy and coma, as well as ataxia, convulsions, and respiratory depression. Studies on pesticide exposure suggest that children may be more prone to central neurologic dysfunction with organophosphate toxicity than adults. Nicotinic effects include muscle fasciculations and twitching, followed by weakness, which can progress to flaccid paralysis as muscles fatigue. Muscarinic effects include miosis, visual blurring, profuse lacrimation, and watery rhinorrhea. Bronchospasm and increased bronchial secretions lead to cough, wheezing, dyspnea, and cyanosis. Cardiovascular manifestations include bradycardia, hypotension, and atroventricular block. Flushing, sweating, salivation, nausea, vomiting, diarrhea, abdominal cramps, and urinary incontinence are also seen. In the absence of prompt intervention, death can quickly result from a combination of central effects and respiratory muscle paralysis.

**Delayed-Onset Neuromuscular Syndrome: Botulism**

The delayed onset (hours to days after exposure) of neuromuscular symptoms is characteristic of botulism. Botulism occurs after exposure to 1 of 7 related neurotoxins produced by certain strains of *Clostridium botulinum*, a strictly anaerobic, spore-forming, Gram-positive bacillus commonly found in soil. Naturally occurring botulism (see Chapter 210) usually follows ingestion of preformed toxin (food poisoning) or results from intestinal toxin production (infantile botulism). An aerosol exposure would likely result in a case of clinical botulism indistinguishable from that caused by natural exposures.

Following exposure to botulinum toxin, clinical manifestations typically begin with bulbar palsies, causing patients to complain of ptosis, photophobia, and blurred vision resulting from difficulty in accommodation. Symptoms can progress to include dysarthria, dysphonia, and dysphagia and, finally, a descending symmetric paralysis. Sensation and sensorium are typically not affected. In the absence of intervention, death often results from respiratory muscle failure.

**Sudden-Onset Respiratory Syndrome: Chlorine, Phosgene, and Cyanide**

The acute onset of respiratory symptoms shortly after exposure should prompt the clinician to consider a range of potential chemical agents. Of note, nerve agents, discussed previously, may affect respiration via massive bronchial hypersecretion, bronchospasm, and respiratory muscle paralysis. However, the nerve agent casualty will likely have generalized muscle involvement and central nervous system manifestations. In contrast, the toxic inhalants chlorine and phosgene produce respiratory distress without neuromuscular involvement.

Chlorine is a dense, acrid, yellow-green gas that is heavier than air. After mild to moderate exposure, ocular and nasal irritation occurs, followed by cough, a choking sensation, bronchospasm, and substernal chest tightness. Pulmonary edema, mediated by hydrochloric acid and free oxygen radical generation, follows moderate to severe exposures within 30 min to several hours. Hypoxemia and hypovolemia secondary to pulmonary edema are the factors responsible for death when it occurs.

Phosgene, like chlorine, is a common industrial compound that was used as a weapon on the battlefields of World War I. Its odor has been described as similar to “new-mown hay.” Like chlorine, phosgene also is thought to result in the generation of hydrochloric acid, contributing particularly to upper airway, nasal, and conjunctival irritation. Acylation reactions caused by the effects of phosgene on the pulmonary alveolar-capillary membrane lead to pulmonary edema. Phosgene lung injury also may be mediated, in part, by an inflammatory reaction associated with leukotriene production. Patients with mild to moderate exposures to phosgene may be asymptomatic, a fact that may cause victims to remain in a contaminated area. Pulmonary edema occurs 4-24 hr after exposure and is dose dependent, with heavier exposures causing earlier symptoms. Dyspnea may precede radiologic findings. In severe exposures, pulmonary edema may be so marked as to result in hypovolemia and hypotension. As in the case of chlorine, death results from hypoxemia and asphyxia.

Cyanide is a cellular poison, with protein clinical manifestations. Initially, cyanide toxicity is most likely to manifest as tachypnea and hyperpnea, progressing rapidly to apnea in cases with significant exposure (see Chapter 63). The efficacy of cyanide as a chemical terrorism agent is limited by its volatility in open air and relatively low lethality in comparison with nerve agents. Released in a closed room, however, cyanide could have devastating effects, as evidenced by its use in the Nazi gas chambers during World War II. Cyanide inhibits cytochrome a, interfering with normal mitochondrial oxidative metabolism and leading to cellular anoxia and lactate acidosis. In addition to respiratory distress, early findings among cyanide victims include tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. With greater exposure, seizures, coma, apnea, and cardiac arrest may follow within min. An elevated anion gap metabolic acidosis is typically
present, and decreased peripheral oxygen utilization leads to an elevated mixed venous oxygen saturation value.

Delayed-Onset Respiratory Syndrome: Anthrax, Plague, Tularemia, and Ricin

A delayed onset of respiratory symptoms (days after exposure) is characteristic of several infectious diseases and is a toxin that might be adapted for sinister purposes by terrorists. Among the most threatening and problematic of these are anthrax, plague, tularemia, and ricin, the latter having garnered considerable media attention in recent years.

Anthrax is caused by infection with the Gram-positive spore-forming rod Bacillus anthracis. Its ability to form a spore enables the anthrax bacillus to survive for long periods in the environment and enhances its potential as a weapon.

The vast majority of naturally occurring anthrax cases are cutaneous, acquired by close contact with the hides, wool, bone, and other by-products of infected ruminants (principally cattle, sheep, and goats). Cutaneous anthrax is amenable to therapy with a variety of antibiotics and is readily recognizable to experienced clinicians in endemic areas; consequently, it is rarely fatal. Although it is common in parts of Asia and sub-Saharan Africa, only 2 cases of cutaneous anthrax had occurred in the United States in the 9 yr that preceded the attacks of 2001 (when 11 cutaneous cases were seen). Gastrointestinal anthrax, which has never been described in the United States, can occur after the ingestion of contaminated meat. In the past, inhalational anthrax, or woolsorters’ disease, was an occupational hazard of abattoir and textile workers. Now eliminated as a naturally occurring disease in the United States, it is this inhalational form of anthrax that poses the greatest terror threat. Following an inadvertent release in 1979 from a biowarfare facility at Sverdlovsk in the former Soviet Union, 66 of 77 (86%) known adult victims of inhalational anthrax died. In the 2001 attacks involving contaminated mail in the United States, 5 of 11 (46%) patients with inhalational anthrax died. Whether better intensive care modalities, changes in antibiotic therapy, or earlier recognition accounted for this improved mortality rate remains unknown.

Symptomatic inhalational anthrax typically begins 1-6 days after exposure, although incubation periods of up to several weeks have been reported. The disease begins as a flu-like illness, characterized by fever, myalgia, headache, and cough. A brief intervening period of improvement sometimes follows, but rapid deterioration then ensues; high fever, dyspnea, cyanosis, and shock mark this second phase. Hemorrhagic meningitis occurs in up to 50% of cases. Chest radiographs obtained late in the course of illness may reveal a widened mediastinum or prominent mediastinal lymphadenopathy; pleural effusions also may be seen. Bacteremia is often so profound that Gram stains of blood disclose the organism at this stage. Prompt treatment is imperative; death occurs in as many as 95% of inhalational anthrax cases if such treatment is begun more than 48 hr after the onset of symptoms.

Whereas inhalational anthrax is a disease primarily of mediastinal lymphatic tissue, exposure to aerosolized plague bacilli typically leads to a primary pneumonia. Endemic plague is usually transmitted via the bites of fleas and is discussed in Chapter 203. The causative organism of all forms of human plague, Yersinia pestis, is a bipolar-staining, Gram-negative facultative intracellular bacillus. An ability to survive for long periods in the environment and enhance its potential as a weapon.

The high degree of infectivity of F. tularensis (<10 organisms are thought to be necessary to produce infection via inhalation), as well as its survivability in the environment, contributes to its inclusion on the list of agents of concern. Several clinical forms of endemic tularemia are known, but inhalational exposure resulting from a terrorist attack would likely lead to a plague-like primary pneumonia or to typhoidal tularemia, manifesting as a variety of nonspecific symptoms including fever, malaise, and abdominal pain.

Ricin is a protein toxin derived from the castor bean plant (Ricinus communis) that inhibits ribosomal protein synthesis. It is highly toxic in animal studies when inhaled and may result in the delayed onset of respiratory distress, pulmonary edema, and acute respiratory failure. One case series of 8 persons from the 1940s described a febrile respiratory illness after inhalational exposure. If injected it may cause a sepsis-like syndrome that may progress to multiorgan system failure; ingestion can lead to severe gastroenteritis. Ricin-containing letters were mailed to a U.S. Senate office building in 2004, and again to President Obama and New York City Mayor Bloomberg in 2013, although no persons were sickened in either attack.

Sudden-Onset Dermatologic Syndrome: Mustard and Lewisite

The development of skin lesions shortly after exposure is characteristic of the chemical vesicants. These compounds, often referred to as blistering agents, are cellular poisons and include the alkylating agent mustard and the organic arsenical agent lewisite. Tissue injury to rapidly reproducing cells begins within minutes of contact with these agents. Clinical effects typically become evident several hours after exposure to mustard, whereas patients exposed to lewisite feel immediate pain. Both mustard and lewisite affect the eyes and respiratory tract and their inadvertent ingestion may produce significant gastrointestinal symptoms. Mustard exposure may lead to bone marrow suppression.

Delayed-Onset Dermatologic Syndrome: Smallpox

The appearance of an exanthem days to weeks after exposure is likely to be a presenting feature of smallpox. Caused by infection with variola virus, a member of the orthopoxvirus family, smallpox has an incubation period of 7-17 days. This would likely permit the wide dispersal of asymptomatic exposed persons, thus contributing to the spread of an outbreak. During the incubation period, virus replicates in the upper respiratory tract. A primary viremia ensues, during which time seeding of the liver and spleen occurs. A secondary viremia then develops, the skin is seeded, and the classic exanthem of smallpox appears. Symptoms of smallpox begin abruptly during the phase of secondary viremia and include fever, rigors, vomiting, headache, backache, and extreme malaise. Within 2-4 days, macules appear on the face and extremities and then progress in synchronous fashion to papules, pustules, and finally scabs. As the scabs separate, survivors often are left with disfiguring, depigmented scars. The synchronous nature of the rash and its centrifugal distribution distinguish smallpox from chick- enpox, which has a centripetal distribution. Historically, smallpox had a 30% mortality rate, with death typically resulting from visceral organ involvement.

DIAGNOSIS

In some cases, the terrorist nature of a chemical or biologic attack may be obvious, for example, a chemical attack in which victims succumb in close temporal and geographic proximity to a dispersal device or terrorists announce their attack. In other instances, the clinician may
need to rely on epidemiologic clues to suspect an intentional release of chemical or biologic agents. The presence of large numbers of victims clustered in time and space should raise the index of suspicion, as should cases of unexpected death or unexpectedly severe disease. Diseases unusual in a given locale, in a given age group, or during a certain season likewise may warrant further investigation. Simultaneous outbreaks of a disease in noncontiguous areas should cause one to consider an intentional release, as should outbreaks of multiple diseases in the same area. Even a single case of a rare disorder such as anthrax or certain viral hemorrhagic fevers would be suspicious, and a single case of smallpox would almost certainly be the result of an intentional dissemination. Large numbers of dying animals might provide evidence of an unnatural aerosol release, as would evidence of disparate attack rates between those known to be indoors and outdoors at a given time.

In a mass casualty setting, diagnoses may be made largely on clinical grounds. The diagnosis of nerve agent intoxication is based primarily on clinical recognition and patient response to antidotal therapy. Several simple rapid detection devices developed for military use can detect the presence of nerve agents. Some of these are now commercially available and are stocked in certain emergency departments and public safety vehicles. Measurements of acetylcholinesterase in plasma or erythrocytes of nerve agent victims may be helpful in long-term prognostication, but correlation between cholinesterase levels and clinical effects is often poor, and the test rarely is available on an emergency basis.

**Botulism** should be suspected clinically among patients presenting with a symmetric, descending, flaccid paralysis. Although the differential diagnosis of botulism includes other uncommon neurologic disorders, such as myasthenia gravis and the Guillain-Barre syndrome, the presence of multiple casualties with similar symptoms should aid in the determination of a botulism outbreak.

Initially, the diagnosis of **cyanide poisoning** also will likely be made on clinical grounds in the presence of the appropriate toxidrome. An unusually high anion gap metabolic acidosis with elevated serum lactate and an oxygen concentration greater than expected in mixed venous blood lend support to the clinical diagnosis. Elevated blood cyanide concentrations can confirm the clinical suspicion.

**Anthrax** should be suspected upon finding Gram-positive bacilli in skin biopsy material (in the case of cutaneous disease), blood smears, pleural fluid, or spinal fluid. Chest radiographs demonstrating a widened mediastinum in the context of fever and constitutional signs, and in the absence of another obvious explanation (e.g., blunt trauma or postsurgical infection), should also lead one to consider the diagnosis. Confirmation can be obtained by blood culture. State health laboratories and federal facilities at the U.S. Centers for Disease Control and Prevention and at the U.S. Army Medical Research Institute of Infectious Diseases can confirm a diagnosis of anthrax by polymerase chain reaction and immunohistochemical assay.

A diagnosis of **plague** can be suspected on finding bipolar “safety-pin”-staining bacilli in Gram or Wayson stains of sputum or aspirated lymph node material; confirmation is obtained by culturing *Y. pestis* from blood, sputum, or lymph node aspirate. The organism grows on standard blood or MacConkey TRA agar but is often misidentified by automated systems. *F. tularensis* grows poorly on standard media; its growth is enhanced on media containing cysteine. Because of its extreme infectivity, however, many laboratories prefer to make a diagnosis via polymerase chain reaction or serologically using an enzyme-linked immunosorbent assay or serum agglutination assay.

**Smallpox** should be suspected on clinical grounds and can be confirmed by culture or electron microscopy of scabs or vesicular fluid, although the manipulation of clinical material from suspected smallpox victims should be attempted only at public health laboratories able to employ maximum biocontainment (Biosafety Level 4) precautions. Similar caution should be exercised with specimens from patients with various viral hemorrhagic fevers.

**PREVENTION**

Preventive measures can be considered in both a preexposure and a postexposure context. **Preexposure protection** against a chemical or biologic attack may consist of physical, chemical, or immunologic measures. **Physical protection** against primary attack often involves gas masks and protective suits; such equipment is used by the military and by certain hazardous materials response teams but it is unlikely to be available to civilians at the precise moment that a release occurs. Medical personnel need to understand the principles of physical protection as they apply to infection control and the spread of contamination.

Pneumonic plague is spread through respiratory droplets. Droplet precautions, including the use of simple surgical masks, are thus warranted for providers caring for patients with plague. Smallpox is transmitted by droplet nuclei. Airborne precautions, including (ideally) a high-efficiency particulate air filter mask, are thus warranted with smallpox victims. Similarly, patients with viral hemorrhagic fever should, in general, be managed with use of contact precautions. Most other biologic agent victims can be safely cared for with use of standard precautions. In the case of chemical agents, residual mustard or nerve agent on the skin or clothing of victims might potentially pose a hazard to medical personnel. For such victims, whenever possible, clothing should be removed and the patients decontaminated using copious amounts of water before extensive medical care is rendered. Most other chemical agents are volatile enough that spread of an agent among patients or from patient to caregiver is unlikely.

**Preexposure chemical prophylaxis** might be used on the basis of credible intelligence reports. Should officials deem that the threatened release of a specific biologic agent appears imminent, antibiotics might be distributed to a population preemptively. Opportunities to employ such a strategy are likely to be limited, although federal and state officials are examining various mechanisms for such employment.

Although licensed vaccines (**preexposure immunologic measures**) against anthrax and smallpox have been developed, widespread use of either vaccine is likely to be problematic, especially in children. The anthrax vaccine is licensed only for those persons age 18 yr and older, is given as a 5 dose series over 18 mo, and requires annual booster doses. These considerations make civilian employment of the current anthrax vaccine on a large scale unlikely, although a new recombinant anthrax vaccine is in development and being studied as a 3 dose series.

Significant obstacles to the widespread employment of smallpox vaccine also exist, although public health officials have contemplated the resumption of a smallpox vaccination campaign. Whereas in the past smallpox vaccine (prepared from vaccinia virus, an orthopoxvirus related to variola) was used safely and successfully in young infants, it has a relatively high rate of serious complications in certain patients. Fetal vaccinia and demise can occur when pregnant women are vaccinated. Vaccinia gangrenosa, an often fatal complication, can occur when immunocompromised persons are vaccinated. Eczema vaccinatum occurs in those with preexisting dermatoses (atopic dermatitis). Severe vaccine-related encephalitis was well known during the era of widespread vaccination; because it occurs only in primary vaccinees, it would disproportionatey affect pediatric patients. Autoinoculation can occur when virus present at the site of vaccination is manually transferred to other areas of skin or to the eye. Young children would presumably be at greater risk for such inadvertent transmission. Myocarditis has been reported following vaccinations of military recruits.

To manage these complications, vaccinia immune globulin should be available when one is undertaking a vaccination campaign. Vaccinia immune globulin (0.6 mg/kg IM) may be given to vaccine recipients who experience severe complications or to significantly immunocompromised individuals exposed to smallpox and in whom vaccination would be unsafe. A compound, ST-246, has been used successfully under an Investigational New Drug permit to treat persons (including children) experiencing severe complications from vaccine. The current cell-culture–derived vaccine (ACAM2000), as well as vaccinia immune globulin and ST-246, can be obtained as needed upon consultation with officials at the Centers for Disease Control and Prevention. In addition to a potential role in preexposure prophylaxis, vaccination may be effective in postexposure prophylaxis if given within the 1st 4 days or so after exposure.
Anthrax vaccine might similarly be employed in a postexposure setting. Some authorities recommend 3 doses of this vaccine as an adjunct to postexposure chemoprophylaxis after documented exposure to aerosolized anthrax spores. Nonetheless, postexposure administration of oral antibiotics constitutes the mainstay of management for asymptomatic victims believed to have been exposed to anthrax as well as to other bacterial agents such as plague and tularemia. Table 723-2 lists appropriate prophylactic regimens for various biologic exposures.

**TREATMENT**

Tables 723-2 and 723-3 provide recommended therapies for overt diseases caused by various chemical and biologic agents. It is likely that the clinician attending to victims will need to make therapeutic decisions before the results of confirmatory diagnostic tests are available and in situations in which the diagnosis is not known with certainty. In particular, decontamination by hospital personnel in appropriate personal protective equipment is required for patients exposed to chemical agents who have not been adequately decontaminated in the prehospital setting (see Table 723-3). In such cases, it is useful to note that many diseases and symptoms caused by chemical and biologic agents will resolve spontaneously, with only supportive care required. Most cases of chlorine or phosgene exposure can be successfully managed by providing meticulous attention to oxygenation and fluid balance. Mustard victims may require intensive multisystem support, but no specific antidote or therapy is available. Many viral diseases, such as smallpox, most viral hemorrhagic fevers, and the equine encephalitides, are also managed supportively.

In addition to ensuring adequate oxygenation, ventilation, and hydration, the clinician may need to provide specific empiric therapies such as smallpox, most viral hemorrhagic fevers, and the equine encephalitides, are also managed supportively.

### Table 723-2 Critical Biologic Agents of Terrorism

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CLINICAL FINDINGS</th>
<th>INCUBATION PERIOD (DAYS)</th>
<th>ISOLATION PRECAUTIONS</th>
<th>INITIAL TREATMENT</th>
<th>PROPHYLAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax (inhaled)*</td>
<td>Patients who are clinically stable after 14 days can be switched to a single oral agent (ciprofloxacin or doxycycline) to complete a 60-days course</td>
<td>1-5</td>
<td>Standard</td>
<td>Ciprofluoxacin1 10-15 mg/kg IV q12h or doxycycline 2.2 mg/kg IV q12h</td>
<td>Ciprofluoxacin 10-15 mg/kg PO q12h or doxycycline 2.2 mg/kg PO q12h</td>
</tr>
<tr>
<td>Plague (pneumonic)</td>
<td>Febrile prodrome with rapid progression to fulminant pneumonia, hemoptysis, sepsis, disseminated intravascular coagulation</td>
<td>2-3</td>
<td>Droplet (for 1st 3 days of therapy)</td>
<td>Gentamicin 2.5 mg/kg IV q8h or doxycycline 2.2 mg/kg IV q12h or ciproflouoxacin 15 mg/kg IV q12h</td>
<td>Doxycycline 2.2 mg/kg PO q12h or ciprofluoxacin 20 mg/kg PO q12h</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Pneumonic: abrupt onset of fever with fulminant pneumonia, Typhoidal: fever, malaise, abdominal pain</td>
<td>2-10</td>
<td>Standard</td>
<td>Same as for plague</td>
<td>Same as for plague</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Febrile prodrome with synchronous, centrifugal, vesiculopustular exanthema</td>
<td>7-17</td>
<td>Airborne (+ contact)</td>
<td>Supportive care</td>
<td>Vaccination may be effective if given within the 1st several days after exposure</td>
</tr>
<tr>
<td>Botulism</td>
<td>Afebrile descending symmetric flaccid paralysis with cranial nerve palsies</td>
<td>1-5</td>
<td>Standard</td>
<td>Supportive care; antitoxin (see text) may halt the progression of symptoms but is unlikely to reverse them</td>
<td>None</td>
</tr>
<tr>
<td>Viral hemorrhagic fevers</td>
<td>Febrile prodrome with rapid progression to shock, purpura, and bleeding diatheses</td>
<td>4-21</td>
<td>Contact (consider airborne in cases of massive hemorrhage)</td>
<td>Supportive care; ribavirin may be beneficial in select cases</td>
<td>None</td>
</tr>
</tbody>
</table>

*In a mass casualty setting, in which resources are severely constrained, it may be necessary to substitute oral therapy for the preferred parenteral option.

1Assuming the organism is sensitive, children may be switched to oral amoxicillin (80 mg/kg/day = q8h) to complete a 60-day course. We recommend that the 1st 14 days of therapy or postexposure prophylaxis, however, include ciprofloxacin and/or doxycycline regardless of age.

2Levofluoxacin or ofloxacine may be an acceptable alternative to ciprofloxacin.

3Rifampin or clarithromycin may be an acceptable alternative to clindamycin as a drug that targets bacterial protein synthesis. If ciprofloxacin or another quinolone is employed, doxycycline may be used as a second agent because it also targets protein synthesis.

4Ampicillin, imipenem, meropenem, or chloramphenicol may be an acceptable alternative to penicillin as a drug with good central nervous system penetration.
Table 723-3 | Critical Chemical Agents of Terrorism

<table>
<thead>
<tr>
<th>AGENT</th>
<th>TOXICITY</th>
<th>CLINICAL FINDINGS</th>
<th>ONSET</th>
<th>DECONTAMINATION*</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NERVE AGENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tabun, sarin, soman, VX</td>
<td>Anticholinesterase: muscarinic, nicotinic, central nervous system effects</td>
<td>Vapor: miosis, rhinorrhea, dyspnea Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea</td>
<td>Seconds: vapor Minutes to hours: liquid</td>
<td>Vapor: fresh air, remove clothes, wash hair Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation</td>
<td>ABCs. Atropine: 0.05 mg/kg IV†, IM‡ (min: 0.1 mg, max: 5 mg), repeat q2-5 min prn for marked secretions, bronchospasm Pralidoxime: 25 mg/kg IV, IM§ (max: 1 g IV; 2 g IM), may repeat within 30-60 min prn, then again q1h for 1 or 2 doses prn for persistent weakness, high atropine requirement Diazepam: 0.3 mg/kg (max: 10 mg) IV; lorazepam: 0.1 mg/kg IV, IM (max: 4 mg); midazolam: 0.2 mg/kg (max: 10 mg) IM prn for seizures or severe exposure</td>
</tr>
</tbody>
</table>

VESICANTS | | | | | |
| Mustard | Alkylation | Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation | Hours | Skin: soap and water Eyes: water (effective only if done within minutes of exposure) | Symptomatic care |
| Lewisite | Arsenical | Immediate pain | | | Possibly British antilewisite (BAL) 3 mg/kg IM q4-6h for systemic effects of lewisite in severe cases |

PULMONARY AGENTS | | | | | |
| Chlorine, phosgene | Liberated hydrochloric acid, alkylation | Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene) | Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema | Fresh air Skin: water | Symptomatic care (see text) |

CYANIDE | | | | | |
| | Cytochrome oxidase Inhibition: cellular anoxia, lactic acidosis | Tachypnea, coma, seizures, apnea | Seconds | Fresh air Skin: soap and water | ABCs, 100% oxygen |

*Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.

†Intraosseous route is likely equivalent to intravenous.

‡Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 723-4.

§Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army’s Mark 1 autoinjector concentration), to effect a reasonable volume for injection. See also Table 723-4.

ABCs, airway, breathing, and circulatory support; max, maximum; min, minimum; prn, as needed.


intravenous administration. Many emergency management services stock military-style autoinjector kits consisting of atropine and 2-PAM for intramuscular injection. Pediatric atropine autoinjectors are licensed, although kits intended for adults (with 2 mg of atropine and 600 mg of pralidoxime) might be used in children >2-3 yr (Table 723-4). Animal studies support the routine prophylactic administration of anticonvulsant doses of benzodiazepines, even in the absence of observable convulsive activity. Delayed neuromuscular symptoms in the setting of terrorism might be due to botulism. Supportive care, with meticulous attention...
A licensed heptavalent antitoxin (types A-G) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 15 min. A second dose (2.5-5 mg/kg IV q12h), or doxycycline (2.2 mg/kg IV q12h) is a reasonable choice. Although naturally occurring strains of B. anthracis usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of B. anthracis exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of Y. pestis and F. tularensis. Concerns about inducible β-lactamases in B. anthracis have led some experts to recommend 1 or 2 additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, imipenem, and clarithromycin are reasonable choices based on in vitro sensitivity data. Because B. anthracis relies on the production of 2 protein toxins, edema toxin, and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningial involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. A combination of ciprofloxacin plus clindamycin plus penicillin G is a good initial empiric therapy for presumed inhalational anthrax. Ciprofloxacin, levofloxacin, or doxycycline monotherapy is probably adequate in cases of cutaneous anthrax, although patients with cutaneous disease resulting from a terrorist attack initially should receive multidrug therapy, because of the possibility of concomitant inhalational exposure.

Raxibacumab, a monoclonal antibody that inhibits anthrax antigen binding to cell receptors, thus preventing toxins from entering cells, is available. It is given prophylactically in high-risk populations or as therapy to patients with cutaneous or inhalational anthrax. The American Red Cross offers a limited stockpile of raxibacumab through the Biodefense & Emerging Threats Program; current CDC guidelines for raxibacumab availability in the United States are at https://www.bt.cdc.gov/raxibacumab/.

The classic cyanide antidote utilizes a nitrite along with sodium thiosulfate and is given in 2 stages. The methemoglobin-forming agent (e.g., sodium nitrite) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 5-10 min. A sulfur donor, such as sodium thiosulfate, is given next. This compound is used as a substrate by the hepatic enzyme rhodanese, which converts cyanide to thiocyanate, a less toxic compound excreted in the urine. Thiosulfate treatment itself is efficacious and relatively benign and may be used alone for mild to moderate cases. Sodium nitrite and sodium thiosulfate are packaged together in standard antidote kits, along with amyl nitrite, a sodium nitrite substitute that can be inhaled in prehospital settings in which intravenous access is not available.

Another antidote available in the United States is hydroxocobalamin with nitrite/thiosulfate-based therapies, many authorities believe that hydroxocobalamin’s efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context.

Animal research suggests a modest benefit of steroid therapy in mitigating lung injury after chlorinated inhalation, and thus steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those manifesting bronchospasm and/or a history of asthma. Further, symptomatic relief has also been reported following chlorine exposure with nebulized 3.75% sodium bicarbonate therapy, though the impact of this regimen on pulmonary damage is unknown. Animal models have also suggested a benefit from antiinflammatory agents, including ibuprofen and N-acetylcysteine, which appear to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), although the results of such interventions have not yet been reported in clinical trials.

In cases in which the delayed onset of respiratory symptoms may be the result of a terrorist attack, consideration should be given to the empirical administration of an antibiotic effective against anthrax, plague, and tularemia. Ciprofloxacin (10-15 mg/kg IV q12h), levofloxacin (8 mg/kg IV q12h), or doxycycline (2.2 mg/kg IV q12h) is a reasonable choice. Although naturally occurring strains of B. anthracis usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of B. anthracis exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of Y. pestis and F. tularensis. Concerns about inducible β-lactamases in B. anthracis have led some experts to recommend 1 or 2 additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, imipenem, and clarithromycin are reasonable choices based on in vitro sensitivity data. Because B. anthracis relies on the production of 2 protein toxins, edema toxin, and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningial involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. A combination of ciprofloxacin plus clindamycin plus penicillin G is a good initial empiric therapy for presumed inhalational anthrax. Ciprofloxacin, levofloxacin, or doxycycline monotherapy is probably adequate in cases of cutaneous anthrax, although patients with cutaneous disease resulting from a terrorist attack initially should receive multidrug therapy, because of the possibility of concomitant inhalational exposure.

Table 723-4  Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care

<table>
<thead>
<tr>
<th>APPROXIMATE AGE</th>
<th>APPROXIMATE WEIGHT (kg)</th>
<th>AUTOINJECTOR SIZE (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>&lt;7.5</td>
<td>0.25</td>
</tr>
<tr>
<td>6 mo-4 yr</td>
<td>7.5-18</td>
<td>0.5</td>
</tr>
<tr>
<td>5-10 yr</td>
<td>18-30</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>&gt;30</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APPROXIMATE AGE (yr)</th>
<th>APPROXIMATE WEIGHT (kg)</th>
<th>NUMBER OF AUTOINJECTORS</th>
<th>PRALIDOXIME DOSE (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-7</td>
<td>13-25</td>
<td>1</td>
<td>24-46</td>
</tr>
<tr>
<td>8-14</td>
<td>26-50</td>
<td>2</td>
<td>24-46</td>
</tr>
<tr>
<td>&gt;14</td>
<td>&gt;50</td>
<td>3</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>

*Consider adult pralidoxime autoinjector use for severely affected mass casualties when IV access or more precise mg/kg IM dosing is logistically impractical. The initial dose using atropine autoinjectors is 1 autoinjector of each recommended size. The initial dose using pralidoxime autoinjectors is the recommended number of adult-intended (600 mg) autoinjectors. These latter may also be injected into an empty sterile vile; the contents redrawn through a filter needle into a small syringe may then provide a ready source of concentrated (300 mg/mL) pralidoxime solution for IM injection to infants. Autoinjectors may become available that provide adult doses of both atropine and pralidoxime in one injector, these could be used in children ≥3 yr in lieu of two individual injectors and dosed as noted above for pralidoxime alone.

Table 723-4: Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care

**ATRO Pine AUTOINJECTOR THERAPY**

<table>
<thead>
<tr>
<th>APPROXIMATE AGE</th>
<th>APPROXIMATE WEIGHT (kg)</th>
<th>AUTOINJECTOR SIZE (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
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<tr>
<td>5-10 yr</td>
<td>18-30</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>&gt;30</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**PRA LIDOXIME AUTOINJECTOR THERAPY**

<table>
<thead>
<tr>
<th>APPROXIMATE AGE (yr)</th>
<th>APPROXIMATE WEIGHT (kg)</th>
<th>NUMBER OF AUTOINJECTORS</th>
<th>PRALIDOXIME DOSE (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-7</td>
<td>13-25</td>
<td>1</td>
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<td>8-14</td>
<td>26-50</td>
<td>2</td>
<td>24-46</td>
</tr>
<tr>
<td>&gt;14</td>
<td>&gt;50</td>
<td>3</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>
approved for the treatment of inhalation anthrax in combination with antibodies. The adult dose is 40 mg/kg given IV over 2 hr and 15 min. The dose for children is weight based; ≤15 kg: 80 mg/kg; >15-50 kg: 60 mg/kg; >50 kg: 40 mg/kg. Premedication with diphenhydramine IV or PO is recommended 1 hr before the infusion.

In patients in whom a diagnosis of plague or tularemia is established, streptomycin (15 mg/kg IM q12h) has historically been considered the drug of choice. Because this drug is generally unavailable, many experts consider gentamicin (2.5 mg/kg IV/IM q8h) the preferred choice for therapy. In addition to ciprofloxacin, levofloxacin, or doxycycline, chloramphenicol (25 mg/kg IV q6h) should be employed in the 6% of pneumonic plague cases with concomitant meningitis. To be effective, therapy for pneumonic plague must be initiated within 24 hr of the onset of symptoms. There is little clinical experience with ricin-induced pulmonary injury. The mainstay of therapy is expected to be supportive care.

The management of vesicant-induced injury is similar to that for burn victims and is largely symptomatic (see Chapter 75). Mustard victims will benefit from the application of soothing skin lotions such as calamine and the administration of analgesics. Early intubation of severely exposed patients is warranted to guard against edematous airway compromise. Oxygen and mechanical ventilation may be needed, and meticulous attention to hydration is of paramount importance. Ongoing research suggests a role for oral N-acetylcysteine in mitigating chronic pulmonary effects due to mustard injury. Lewisite victims can be managed in much the same manner as mustard victims. In addition, dimercaprol (British antilewisite) in oil, given intramuscularly, may help ameliorate the systemic effects of lewisite.

The management of symptomatic smallpox victims also is largely supportive, with attention to pain control, hydration status, and respiratory sufficiency again of primary importance. The parenteral antiviral compound cidofovir, licensed for the treatment of cytomegalovirus retinitis in HIV-infected patients, has in vitro efficacy against variola and other orthopoxviruses. Its utility in treating smallpox victims is untested. Moreover, in the face of a large outbreak of disease, wide parenteral use of this drug would be problematic. ST-246, mentioned previously, demonstrates excellent in vitro activity against orthopoxviruses, but its utility in treating patients with smallpox is likewise untested.

Bibliography is available at Expert Consult.
Bibliography


by dogs, pigs, and horses. Approximately 1% of dog bite wounds and 6% of cat bite wounds in the United States require hospitalization. During the past 3 decades, there have been approximately 20 deaths per year in the United States from dog-inflicted injuries; 65% of these occurred in children < age 11 yr. The breed of dog involved in attacks on children varies; Table 724-1 depicts the risk index of fatal dog bites by breed. Compared with other breeds, bites by pit bulls account for higher rates of hospital admission, higher Glasgow scores at admission, and an increased risk of death. Unaltered male dogs account for approximately 75% of attacks; nursing dams often inflict injury to humans when children attempt to handle their puppies.

The majority of dog attacks on children in the United States occur between the ages of 6 and 11 yr, with a slight predominance of males. Approximately 65% of the attacks occur around the home, 75% of the biting animals are known by the children, and almost 50% of the attacks are said to be unprovoked. Similar statistics apply in Canada, where 70% of all bites reported in 1 study were sustained by children between ages 2 and 14 yr; 65% of the dogs involved in the biting were part of the family or extended family, and the bite occurred in someone’s home.

Of the approximately 450,000 reported cat bites per year occurring in the United States, nearly all are inflicted by known household animals. Because rodent bites (rat, mouse, gerbil) do not represent reportable conditions, little is known about the epidemiology of these injuries or the incidence of infection after rodent-inflicted bites or scratches.

Few data exist on the incidence and demographics of human bite injuries in pediatric patients; however, preschool and early school-age children appear to be at greatest risk of sustaining an injury from human bites, often in daycare or preschool settings. In some series, the proportion of human bites is highest among adolescents, an age group in which fist-to-tooth injuries (so-called fight bites) become more common.

**CLINICAL MANIFESTATIONS**

Dog bite–related injuries can be divided into 3 categories of almost equal incidence: abrasions, puncture wounds, and lacerations with or without an associated avulsion of tissue. Dog bites may also involve crush injury to tissues. In contrast, the most common type of injury from cat and rat bites is a puncture wound. Cat bites often penetrate to deep tissue. Human bite injuries are of 2 types: an occlusion injury that is incurred when the upper and lower teeth come together on a body part, or a clenched-fist injury that occurs when the injured fist, usually on the dominant hand, strikes the teeth of another individual.

**DIAGNOSIS**

Management of the bite victim should begin with a thorough history and physical examination. Careful attention should be paid to the circumstances surrounding the bite event (e.g., species and number of animals, type of animal [domestic or wild], whether the attack was provoked or unprovoked, location of the attack); a history of drug allergies; and the immunization status of the child (tetanus) and animal (rabies). During physical examination, meticulous attention should be paid to the type, size, and depth of the injury; the presence of any foreign material in the wound; the status of underlying structures; and, when the bite is on an extremity, the exact location of the injury, an assessment of possibly involved structures, and the range of motion of the affected area. A diagram of the injury should be recorded in the patient’s medical record. Radiographs of the affected part should be considered if there is likelihood that a bone or joint was penetrated or fractured, or if foreign material is present. The possibility of a fracture or penetrating injury of the skull should particularly be considered in infants who have sustained dog bite injuries to the face or head.

**COMPLICATIONS**

Infection is the most common complication of bite injuries, regardless of the species of biting animal. The decision to obtain material for culture from a wound depends on the species of the biting animal, the
length of time that has elapsed since the injury, the depth of the wound, the presence of foreign material contaminating the wound, and whether there is clinical evidence of infection. Although potentially pathogenic bacteria have been isolated from up to 80% of dog bite wounds that are brought to medical attention within 8 hr after the bite, the infection rate for wounds receiving medical attention in <8 hr is relatively low (2.5–20%). If the dog bite(s) is(are) not deep and/or extensive, wounds that are <8 hr old do not require cultures unless there are early signs of infection or the patient is immunocompromised. *Capnocytophaga canimorsus* is isolated from approximately 5% of infected wounds in immunocompromised patients and can cause serious systemic infection in these individuals. The infection rate in cat bite wounds, even those that receive prompt medical attention, is >50%; therefore, it is prudent to obtain material for culture from all but the most trivial cat-bite wounds. Cultures should be taken from all other animal bite wounds that are not brought to medical attention within 8 hr, regardless of species.

The rate of infection after rodent bite injuries is not known. Most of the oral flora of rats is similar to that of other mammals; however, approximately 50% and 25% of rats harbor strains of *Streptobacillus moniliformis* and *Spirillum minus*, respectively, both of which cause rat bite fever (see Chapter 724.1).

All human bite wounds, regardless of the mechanism of injury, should be regarded as carrying a high risk for infection and should be cultured. Because of the high incidence of anaerobic infection after bite wounds, it is important to obtain material for anaerobic as well as aerobic cultures.

**TREATMENT**

Table 724-3 describes the prophylactic management of human or animal bite wounds to prevent infection.

After appropriate material has been obtained for culture, the wound should be anesthetized, cleaned, and vigorously irrigated with copious amounts of sterile saline. Irrigation with antibiotic-containing solutions provides no advantage over irrigation with saline alone and may cause local irritation of the tissues. Puncture wounds should be thoroughly cleansed and gently irrigated with a catheter or blunt-tipped needle; high-pressure irrigation should not be employed. Avulsed or devitalized tissue should be debrided and any fluctuant areas incised and drained.

Insufficient data exist to settle questions of whether bite wounds should undergo primary closure, delayed primary closure (3–5 days), or healing by secondary intention. Factors to be considered are the type, size, and depth of the wound; the anatomic location; the presence of infection; the time since the injury; and the potential for cosmetic disfigurement. Appropriate surgical consultation (e.g., general pediatric surgery; plastic, hand, or orthopedic surgery) should be obtained for all patients with deep or extensive wounds; wounds involving the hands, face, or bones and joints; and infected wounds that require open drainage. Although there is general agreement that visibly infected wounds and those that are more than 24 hr old should not be sutured, there is variation in practice regarding the efficacy and safety of closing wounds <8 hr old with no evidence of infection. Because all hand wounds are at high risk for infection, particularly if there has been disruption of the tendons or penetration of the bones, surgical

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**Table 724-1** Breed of Dog Associated with Involvement in Fatal Attacks, 2007 National Registration Data from the American Kennel Club, and Relative Risk of Fatal Attack

<table>
<thead>
<tr>
<th>BREED</th>
<th>NUMBER OF DOGS INVOLVED IN FATAL ATTACKS</th>
<th>NUMBER OF DOGS REGISTERED AKC</th>
<th>RELATIVE RISK OF FATAL ATTACK PER DOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pit Bull</td>
<td>113</td>
<td>2239</td>
<td>2520</td>
</tr>
<tr>
<td>Neapolitan Mastiff</td>
<td>2</td>
<td>357</td>
<td>280</td>
</tr>
<tr>
<td>Chow Chow</td>
<td>2</td>
<td>1567</td>
<td>65</td>
</tr>
<tr>
<td>Rottweiler</td>
<td>18</td>
<td>14,211</td>
<td>65</td>
</tr>
<tr>
<td>Great Pyrenees</td>
<td>2</td>
<td>1916</td>
<td>50</td>
</tr>
<tr>
<td>Parson Russell Terrier</td>
<td>1</td>
<td>1096</td>
<td>45</td>
</tr>
<tr>
<td>Old English Sheepdog</td>
<td>1</td>
<td>1206</td>
<td>40</td>
</tr>
<tr>
<td>Siberian Husky</td>
<td>6</td>
<td>9048</td>
<td>35</td>
</tr>
<tr>
<td>Bullmastiff</td>
<td>1</td>
<td>3735</td>
<td>15</td>
</tr>
<tr>
<td>Doberman Pinscher</td>
<td>2</td>
<td>11,381</td>
<td>10</td>
</tr>
<tr>
<td>Australian Shepherd or Mix</td>
<td>1</td>
<td>6471</td>
<td>10</td>
</tr>
<tr>
<td>Mastiff Mix</td>
<td>1</td>
<td>7160</td>
<td>5</td>
</tr>
<tr>
<td>German Shepherd Dog</td>
<td>4</td>
<td>43,376</td>
<td>5</td>
</tr>
<tr>
<td>Boxer</td>
<td>1</td>
<td>33,548</td>
<td>1.5</td>
</tr>
<tr>
<td>Golden Retriever or Mix</td>
<td>1</td>
<td>39,659</td>
<td>1.5</td>
</tr>
<tr>
<td>Labrador Retriever or Mix</td>
<td>2</td>
<td>114,110</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>158</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data presented only for dog breeds for which registration information is available from the American Kennel Club (AKC). The AKC does not register the Perro de Presa Canario, Wolf Hybrids, or dogs of unknown mixed breed.

†The term pit bull refers to dogs from the following breeds: American Pit Bull Terrier, American Staffordshire Terrier, and Staffordshire Bull Terrier.

‡Data for Labrador Retrievers and Labrador Mix are combined. Relative Risk is normalized to Labrador Retriever and Labrador Mix.

Microorganisms Associated with Bites

<table>
<thead>
<tr>
<th>Category of Bites</th>
<th>Microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOG BITES</td>
<td>Staphylococcus species, Streptococcus species, Eikenella species, Pasteurella species, Proteus species, Klebsiella species, Haemophilus species, Enterobacter species, Capnocytophaga canimorsus, Bacteroides species, Moraxella species, Corynebacterium species, Neisseria species, Fusobacterium species, Prevotella species, Porphyromonas species</td>
</tr>
<tr>
<td>CAT BITE</td>
<td>Pasteurella species, Actinomyces species, Propionibacterium species, Bacteroides species, Fusobacterium species, Clostridium species, Wolinella species, Peptostreptococcus species, Staphylococcus species, Streptococcus species</td>
</tr>
<tr>
<td>HERBIVORE BITES</td>
<td>Actinobacillus lignieresii, Actinobacillus suis, Pasteurella multocida, Pasteurella caballi, Staphylococcus hyicus subsp. hyicus</td>
</tr>
<tr>
<td>SWINE BITES</td>
<td>Pasteurella aerogenes, Pasteurella multocida, Bacteroides species, Proteus species, Actinobacillus suis, Streptococcus species, Flavobacterium species, Mycoplasma species</td>
</tr>
<tr>
<td>RODENT BITES—RAT BITE</td>
<td>Clostridium perfringens, Erysipelothrix rhusiopathiae, Pseudomonas aeruginosa, Enterococcus species, Staphylococcus species, Streptococcus species</td>
</tr>
</tbody>
</table>

Cleansing
- Remove visible dirt.
- Cleanse the wound surface with soap and water, saline, 1% povidone–iodine, or 1% benzalkonium chloride.
- Irrigate with a copious volume of sterile saline solution by high-pressure syringe irrigation.
- Do not irrigate puncture wounds; Standard Precautions should be used.

Wound culture
- No, for fresh wounds, unless signs of infection exist.
- Yes for wounds that appear infected.

Diagnostic Imaging
- Indicated for penetrating injuries involving bones or joints, for suspected fracture, or to assess foreign body inoculation.

Debridement
- Remove superficial devitalized tissue.

Operative debridement and exploration
- Yes if any of the following:
  - Extensive wounds (devitalized tissue)
  - Involvement of the metacarpophalangeal joint (clenched-fist injury)
  - Cranial bites by large animal

Wound closure
- Yes for selected fresh, nonpuncture bite wounds.

Assess tetanus immunization status
- Yes.

Assess risk of rabies from animal bites
- Yes.

Assess risk of hepatitis B virus infection from human bites
- Yes.

Assess risk of human immunodeficiency virus from human bites
- Yes.

Initiate antimicrobial therapy
- Yes for:
  - Moderate or severe bite wounds, especially if edema or crush injury is present
  - Puncture wounds, especially if penetration of bone, tendon sheath, or joint has occurred
  - Face, hand, foot, and genital bites
  - Wounds in immunocompromised and asplenic persons
  - Wounds with signs of infection

Follow-up
- Inspect wound for signs of infection within 48 hr

*Use of an 18-gauge needle with a large-volume syringe is effective. Antimicrobial or antiinfective solutions offer no advantage and may increase tissue irritation.

Both aerobic and anaerobic bacterial culture should be performed.

therapy for human and animal bite wounds, because of its activity against most bacteria that have been isolated from infected bites. Similarly, ticarcillin–clavulanate or ampicillin–sulbactam is preferred for patients who require empirical parenteral therapy. Penicillin G remains the drug of choice for prophylaxis and treatment of rat-inflicted injuries, as this agent has excellent activity against S. moniliformis and S. minor. Because 1st-generation cephalosporins have limited activity against P. multocida and E. corrodens, they should not be used for prophylaxis or empirical initial therapy of bite wound infections. Therapeutic alternatives for penicillin-allergic patients are limited, because the traditional alternative agents are generally inactive against 1 or more of the multiple pathogens that cause bite wound infections. Clindamycin plus trimethoprim–sulfamethoxazole is the most commonly suggested regimen for these patients. Tetracycline is the drug of choice for penicillin-allergic patients who have sustained rat bite injuries.

Although tetanus occurs only rarely after human or animal bite injuries, it is important to obtain a careful immunization history and to provide tetanus toxoid to all patients who are incompletely immunized or in whom it has been longer than 5 yr since the last tetanus immunization. The need for postexposure rabies vaccination in victims of dog and cat bites depends on whether the biting animal is known to have been vaccinated and, most importantly, on local experience with rabid animals in the community. Bites from bats, foxes, skunks, and raccoons should be considered to carry a high risk of rabies, and postexposure prophylaxis should be indicated. If a biting dog or cat has escaped, a decision about rabies prophylaxis can be based on the circumstances surrounding the bite and advice from local infectious diseases specialists and/or health department officials. Annually worldwide, animal bites and contacts result in more than 10 million postexposure courses. Postexposure prophylaxis for hepatitis B should be considered in the rare instance in which a susceptible individual has sustained a human bite from an individual who is at high risk for hepatitis B.

PREVENTION

It is possible to reduce the risk of animal bite injury with anticipatory guidance (Table 724-4). Parents should be routinely counseled during prenatal visits and routine health maintenance examinations about the risks of having potentially biting pets in the household. All patients should be cautioned against harboring exotic animals for pets. Additionally, parents should be made aware of the proclivity of certain breeds of dogs to inflict serious injuries and the protective instincts of nursing dams. All young children should be closely supervised, particularly when in the presence of animals, and from a very early age should be taught to respect animals and to be aware of their potential to inflict injury. Reduction of the rate of human bite injuries, particularly in daycare centers and schools, can be achieved by good surveillance of the children and adequate teacher:child ratios.

Bibliography is available at Expert Consult.

724.1 Rat Bite Fever

Charles M. Ginsburg and David A. Hunstad

ETIOLOGY

Rat bite fever is a generic term that has been applied to at least 2 distinct clinical syndromes, each caused by a different microbial agent. Rat bite fever caused by S. moniliformis is most commonly reported in the United States, as well as in Brazil, Canada, Mexico, Paraguay, Great Britain, and France; it has been identified elsewhere in Europe and in Australia. S. moniliformis is a Gram-negative bacillus that is present in the nasopharyngeal flora of many laboratory and wild rats. Infection with S. moniliformis most commonly occurs following the bite of a rat; however, infection has also been reported in individuals who have been scratched by rats, in those who have handled dead rats, and in those who have ingested milk contaminated with the bacterium (termed Haverhill fever). Rat bite fever may also be transmitted by bites from wild mice. Rat bite fever caused by S. minus, called siodoku, is most commonly reported in Asia. S. minus is a small, spiral, aerobic Gram-negative organism. Reports of rat bite fever from Africa are rare, suggesting underrecognition rather than absence of the disease.

CLINICAL COURSE

The incubation period for the streptobacillary form of rat bite fever is variable, ranging from 3–10 days. The illness is characterized by an abrupt onset of fever up to 41°C (105.8°F) (fever occurring in more than 90% of reported cases), severe throbbing headache, intense myalgia, chills, and vomiting. In virtually all instances, the lesion at the cutaneous inoculation site has healed by the time the systemic symptoms first appear. Shortly after the onset of the fever, a polymorphous rash occurs in up to 75% of patients. In most patients, the rash consists of blotchy, red maculopapular lesions that often have a petechial component; the distribution of the rash is variable but is typically most dense on the extremities. Hemorrhagic vesicles may develop on the hands and feet and are very tender to palpation (Fig. 724-1). Approximately 50% of patients have arthritis, which first manifests toward the end of the 1st wk of disease; early on, the arthritis may be migratory. If untreated, fever, rash, and arthritis last from 14–21 days, often with a biphasic pattern to the fever and arthritis. A wide range of complications are reported in patients with rat bite fever, the most common being pneumonia, persistent arthritis, brain and soft tissue abscesses, and, less commonly, myocarditis or endocarditis. The mortality rate of untreated rat bite fever is estimated to be approximately 13%.

The incubation period of siodoku is longer (14–21 days) than that of the streptobacillary form of disease. The hallmark of Spirillum-induced

Table 724-4 Measures for Preventing Dog Bites

- Realistically evaluate environment and lifestyle and consult with a professional (e.g., veterinarian, animal behaviorist, or responsible breeder) to determine suitable breeds of dogs for consideration.
- Dogs with histories of aggression are inappropriate in households with children.
- Be sensitive to cues that a child is fearful or apprehensive about a dog and, if so, delay acquiring a dog.
- Spend time with a dog before buying or adopting it. Use caution when bringing a dog or puppy into the home of an infant or toddler.
- Spay/neuter virtually all dogs (this frequently reduces aggressive tendencies).
- Never leave infants or young children alone with any dog.
- Properly socialize and train any dog entering the household.
- Teach the dog submissive behaviors (e.g., rolling over to expose abdomen and relinquishing food without growling).
- Immediately seek professional advice (e.g., from veterinarians, animal behaviorists, or responsible breeders) if the dog develops aggressive or undesirable behaviors.
- Do not play aggressive games with your dog (e.g., wrestling).
- Teach children basic safety around dogs and review regularly:
  - Never approach an unfamiliar dog.
  - Never run from a dog and scream.
  - Remain motionless when approached by an unfamiliar dog (e.g., “be still like a tree”).
  - If knocked over by a dog, roll into a ball and lie still (e.g., “be still like a log”).
  - Never play with a dog unless supervised by an adult.
  - Immediately report stray dogs or dogs displaying unusual behavior to an adult.
  - Avoid direct eye contact with a dog.
  - Do not disturb a dog who is sleeping, eating, or caring for puppies.
  - Do not pet a dog without allowing it to see and sniff you first.
  - If bitten, immediately report the bite to an adult.

Bibliography
disease is fever associated with an indurated, often suppurative, non-healing lesion at the bite site. Lymphadenitis and lymphadenopathy invariably are present in the regional nodes that drain the inoculation site, and many patients have a generalized macular rash most prominent when fever is present. In untreated patients, sodoku has a relapsing and remitting course; symptoms abate after 5-7 days of chills and fever but recur 7-10 days later. There may be multiple cycles if the disease is not recognized and treated.

**DIAGNOSIS**

Diagnosis of the streptobacillary form of rat bite fever is difficult, because the disease is uncommon and can be confused with Rocky Mountain spotted fever or (less commonly) meningococcemia. Furthermore, *S. moniliformis* is difficult both to isolate and to identify with classic bacteriologic techniques. The organism is fastidious, requires enriched media for growth, and is inhibited by sodium polyanethol sulfonate, an additive present in many commercial blood culture bottles. A definitive diagnosis is made when the organism is recovered from blood or joint fluid or is identified in human samples with molecular technology such as polymerase chain reaction analysis, which has been used successfully in humans and laboratory animals.

Diagnosis of sodoku is made on clinical grounds, because there are no diagnostic serologic tests and *S. minus* has not been cultured on artificial media. Rarely, the organism may be identified in Gram-stained smears of pus from the inoculation site.

**TREATMENT**

Penicillin is the drug of choice for both forms of rat bite fever. Intravenous penicillin G or intramuscular penicillin G procaine is recommended for 7-10 days; a regimen of IV penicillin G for 5-7 days followed by oral penicillin V for an additional 7 days has also been used. Doxycycline, gentamicin, or streptomycin represent effective alternatives for penicillin-allergic patients. Patients with endocarditis caused by *S. moniliformis* require high-dose penicillin G for 4 wk; the addition of streptomycin or gentamicin might be helpful.

*Bibliography is available at Expert Consult.*

### 724.2 Monkeypox

**Charles M. Ginsburg and David A. Hunstad**

#### ETIOLOGY

Monkeypox virus, causing the disease monkeypox, is the most important member for humans of the genus *Orthopoxvirus* since the eradication of smallpox (variola). Monkeys are the predominant host for the virus; however, it may be endemic in African rainforest squirrels and is present in African rats, mice, domestic pigs, hedgehogs, and opossums. It also has been identified in and transmitted by prairie dogs in the United States, and has affected elephants in zoos. Severity of infection varies by viral strain and by host; for example, disease is relatively mild in cynomolgus monkeys but severe in orangutans.

Monkeypox virus was first observed in humans from West and Central Africa in the 1970s at the time that smallpox had been eradicated from the area. In the 1970s, the secondary attack rate was around 3% (a stark comparison to the 80% seen in unvaccinated smallpox contacts). Few cases were observed over the next 2 decades; however, during a subsequent outbreak in the 1990s when immunity to smallpox was no longer prevalent in the population, the secondary attack rate exceeded 75%. Monkeypox outbreaks have also been reported in the Sudan. Monkeypox was inadvertently introduced into the United States in 2003, presumably through rodents from Ghana that infected prairie dogs who were distributed as pets; this outbreak affected more than 70 persons. Primary transmission of the disease from infected animal to human is by bite or by human contact with an infected animal’s blood, wound discharge, or other body fluids. Human-to-human transmission of infection is uncommon but is believed to have been an important source for transmission of new cases during the United States outbreak.

#### CLINICAL COURSE

The clinical signs, symptoms, and course of monkeypox are similar to those of smallpox, although typically milder. After a 10-14 day incubation period during which the virus replicates in lymphoid tissues, humans experience an abrupt onset of malaise, fever, myalgia, headache, and severe backache. Nonproductive cough, nausea, vomiting, and abdominal pain may be present. Generalized lymphadenopathy, a finding unusual in smallpox, is invariably present during the acute stages of monkeypox illness. After a 2-4 day prodrome, an exanthem appears in cephalad-to-caudal progression. As the rash progresses, fevers begin to abate. The rash is initially macular, but transforms within hours to firm papules that rapidly vesiculate and become pus-filled over 2-3 days. Unlike smallpox lesions, but similar to chickenpox lesions, the lesions of monkeypox tend to occur in crops (Fig. 724-2). Late into the 2nd wk of illness, the lesions begin to desiccate, crust, scab, and fall off.

Monkeypox should be suspected in any child who has the characteristic prodrome associated with an atypical form of chickenpox and a history of contact with prairie dogs or exotic mammals such as Gambian rats and rope squirrels. Diagnosis is by isolation of monkeypox virus in culture, demonstration by polymerase chain reaction of viral DNA in a clinical specimen, or microscopic demonstration of an orthopoxvirus in a clinical specimen in the absence of other orthopoxvirus exposure.

#### TREATMENT

There is no proven effective therapy for monkeypox. Despite evidence that preexposure administration of smallpox vaccine is 85% effective in preventing or attenuating monkeypox disease, the rarity of monkeypox infection does not warrant universal vaccination. In instances of known exposure or in outbreak situations, there may be an indication...
Bibliography


for administering smallpox vaccine. Consideration should be given to vaccinating close family contacts and health care workers who provide care to infected individuals. Vaccine is said to be preventive if given within 2 wk of exposure. Individuals with a compromised immune system and those with life-threatening allergies to latex or to smallpox vaccine or any of its components (polymyxin B, streptomycin, tetracycline, neomycin) also should not receive smallpox vaccine.

Although there are data indicating that cidofovir has in vitro activity against monkeypox virus and has been effective in preventing monkeypox infection in animals, there are no data to support its effectiveness in humans. Careful attention should be paid to skin hygiene, maintenance of adequate nutrition and hydration, and prompt implementation of local or systemic therapy of secondary bacterial infection that may occur. For prevention of human-to-human spread of disease, a combination of contact, droplet, and airborne infection control procedures should be implemented.

*Bibliography is available at Expert Consult.*
Bibliography


Not every bite from a venomous creature is harmful. In many cases no venom is injected, so-called dry bites. A dry bite may occur for many reasons, including failure of the venom delivery mechanism and depletion of venom. Up to 20% of pit viper, 80% of coral snake, and approximately 50% of all venomous snake bites are dry.

In the 2011 report of the American Association of Poison Control Centers, more than 60,000 consultations were related to bites and stings of various creatures, with approximately one third involving victims < age 19 yr. There were 2 deaths, both from snake bites in adult males, 1 from the genera *Crotalus* (rattlesnake) and 1 from the genera *Agkistrodon* (copperhead or cottonmouth).

**GENERAL APPROACH TO THE ENVENOMATED CHILD**

Children may be bitten or stung as they play and explore their environment. The evaluation may be hampered by an unclear history of the circumstances and the possible offending organism, particularly with preverbal children. The overall effects of some venomous bites and stings may be relatively more severe in children than in adults, because children generally receive a similar venom load from the offending animal yet have less circulating blood volume to dilute its effects.

**General Management**

When faced with an envenomated child, the treating physician should anticipate a dynamic clinical syndrome that may progress with time, with important, potentially subtle, findings. Treatment of an envenomated child should start with assessing and managing as necessary the airway, breathing, and circulation (ABCs). Most envenomations require little more than local wound care, pain control, reassurance, and possibly observation. The severely envenomated child may need airway and respiratory protection and support (e.g., high-concentration oxygen administration and endotracheal intubation) and adequate IV access in an unaffected extremity if possible (see Chapters 70 and 71). Early hypotension tends to be related to vasodilation and should be treated with volume expansion using appropriate infusion of physiologic saline solutions (normal saline boluses of 20 mL/kg body weight; repeated as needed up to 3 times). Shock unresponsive to volume repletion may require addition of a vasoactive pharmacologic agent such as epinephrine or dopamine (in addition to antivenom administration as appropriate). If the presentation is suspicious for an anaphylactic reaction to venom, appropriate treatment (including epinephrine) should be initiated as soon as possible (see Chapter 149). Occasionally,
it is difficult to determine the precise etiology for sudden collapse after a venomous bite or sting—venom toxicity vs anaphylaxis. In such cases, treatment for both should be started.

The affected body part should be immobilized in a position of function and any areas of edema should be marked, measured, and monitored. If antivenom (AV) is available for the envenomation, efforts should be initiated to locate and secure an adequate amount to treat the patient (at least a starting dose). In the United States, regional poison control centers can facilitate this effort and are especially helpful if the offending species is exotic. Guidance in dosing the appropriate AV can generally be found in the package insert that accompanies the agent, although the advice in inserts for some products from developing countries may contain inaccurate and incorrect recommendations. Physicians who do not regularly treat venomous bites and stings should consult local or regional experts for assistance.

Antivenom Administration
Specific AVs are available for many venomous creatures of the world, particularly snakes, spiders, and scorpions. These products essentially impart passive immunity to the victim and should be given in cases of significant envenomation as early in the process as possible, because AV is capable of neutralizing only circulating, unbound venom components in the blood.

AVs may be either in liquid form or lyophilized (requiring reconstitution prior to administration). Most AVs are given intravenously. There is no benefit to giving any AV locally at the bite site. As soon as the need for AV is established, it should be placed into solution (generally diluted in a quantity of normal saline equivalent to 20 mL/kg body weight, up to 250–1,000 mL total).

As heterologous serum products, AVs carry some variable risk of inducing nonallergic or allergic anaphylactic reactions. Therefore, the patient should be closely monitored, and a physician should be present during the infusion, with access to all the appropriate equipment and medications needed to reverse such a reaction. Skin tests, often recommended by AV manufacturers, are unreliable and should be omitted.

Intravenous AV should be started slowly, and the rate gradually increased as tolerated by the patient, with a goal to administer the entire dose in approximately 1 hr.

If the victim experiences a reaction to the product, it should be temporarily stopped. Intramuscular epinephrine and intravenous antihistamines and steroids should be given. Then the AV should be restarted, possibly at a slower rate and in a more dilute solution. If the reaction is severe, the decision must be made as to whether the benefits of AV outweigh the risks of anaphylaxis on the basis of the patient’s clinical condition. If AV is deemed critical for the patient’s survival despite the occurrence of anaphylaxis, the patient should be placed in an intensive care setting with close, possibly invasive, monitoring, and should receive simultaneous administration of AV and an epinephrine infusion.

AV can also cause delayed immunoglobulin G and M–mediated serum sickness in some patients (see Chapter 150). Serum sickness occurs 0–2 wk after AV administration, manifesting as fever, myalgias, arthralgias, urticaria, and potential renal and neurologic involvement. It is easily treated with oral steroids, antihistamines, and acetaminophen.

General Wound Care
Bites and stings require basic wound care, including copious tap water or normal saline irrigation under pressure when possible. For small puncture wounds this is impractical, but the skin should still be cleaned with soap and water. Tetanus immunization should be updated as needed. Intact blisters should be left to act as natural bandages and help prevent infection, whereas broken blisters should be debrided. Exposed tissue should be covered with wet to dry dressings. Necrotic wounds, such as those that might follow some snake and spider bites, should be judiciously debrided, with removal of only clearly necrotic tissue. Reconstructive surgery with skin grafts or muscle/tendon grafts may be necessary. Prophylactic antibiotics are not necessary except, perhaps, in cases in which an ill-informed “rescuer” cut into the bite and applied mouth suction. Antibiotics should generally be reserved for signs of established secondary infection.

SNAKE BITES
Most snake bites are inflicted by nonvenomous species and are of no more consequence than a potentially contaminated puncture wound (Fig. 725-1). Venomous snakes, however, kill many tens of thousands of people in the world each year. The precise number is difficult to ascertain, because the toll in human suffering is far greater in developing nations. Developed nations, with established medical care systems, have relatively few fatalities each year.

Most of the world’s medically significant venomous snakes belong to 1 of 2 families—Viperidae and Elapidae (Table 725-1). In developing nations, most snake envenomations occur in agricultural workers who inadvertently contact snakes while in the fields. Many victims of snake envenomation in developed nations are adolescent or young adult males, frequently intoxicated, who are attempting to handle or catch the snake. Bites are located on an extremity in more than 95% of cases. In the United States, approximately 98% of venomous snake bites are inflicted by pit vipers (family Viperidae; subfamily Crotalinae). A small fraction of bites are caused by coral snakes (family Elapidae) in the South and Southwest, and by exotic snakes that have been imported.

Venoms and Effects
Snake venoms are complex mixtures of proteins including large enzymes that cause local tissue destruction and low-molecular-weight polypeptides that have the more lethal systemic effects. The symptoms and severity of an envenomation vary according to the type of snake, the amount of venom injected, and the location of the bite. The fear caused by a snake bite can result in nausea, vomiting, diarrhea, cold clammy skin, and even syncope regardless of whether or not venom was injected. In general, viper venoms can have deleterious effects on almost any organ system. Most viper bites cause significant local pain, swelling, and ecchymosis and may result in variable necrosis of the bitten extremity (Fig. 725-2). The pain and swelling typically begin quickly after the bite and progress over hours to days. Serious envenomations may result in a consumptive coagulopathy, hypotension, and respiratory distress. In contrast, venoms from the Elapidae tend to be more neurotoxic with little or no local tissue damage. These bites cause variable local pain and the onset of systemic effects can be delayed for hours. Manifestations of neurotoxicity generally are caused by curare-like blockade at the neuromuscular junction. Symptoms usually begin with cranial nerve palsies such as ptosis, dysarthria, and dysphagia and may progress to respiratory failure and complete paralysis. There are exceptions; some members of the Elapidae family cause little or no neurotoxicity but rather severe tissue necrosis (e.g., African spitting cobra). Some vipers, including the southern Pacific rattlesnake (Crotalus oreganus helleri), western diamondback rattlesnake (Crotalus atrox), timber rattlesnake (Crotalus horridus horridus), and some populations of the Mohave rattlesnake (Crotalus scutulatus), cause significant neurotoxicity. Physicians should proactively learn the important species in their regions, including how the species can be identified, the expected effects of their venoms, and proper approaches to management.

Management
Prehospital care should focus on rapid transport to the emergency department while supporting the victim’s vital signs as needed. Constrictive clothing, jewelry, and watches should be removed, and the injured body part should be immobilized in a position of function at the level of the heart. All proposed field treatments for snake bites, such as tourniquets, ice, electric shock, incision, and suction, have proven problematic, with most being ineffective and deleterious.

At the hospital, attention is directed to the ABCs and supportive care as needed. An effort should be made to identify the offending snake and then to secure the appropriate AV. Intravenous access should be established in an unaffected extremity, and standard laboratory specimens should be obtained, including those for a complete blood count, coagulation studies, fibrinogen concentration, and serum chemistry
Figure 725-1 Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States. (Note: the northern Pacific rattlesnake is now classified as *Crotalus oreganus oreganus*.) (Modified from Adams JG, et al, editors: Emergency medicine, Philadelphia, 2008, WB Saunders. Drawing by Marlin Sawyer.)

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>VENOMOUS?</th>
<th>LOCATION</th>
<th>EXAMPLES</th>
<th>TOXIN EFFECTS/OTHER COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colubridae</td>
<td>Some species</td>
<td>Most parts of the world</td>
<td>Garter snakes (<em>Thamnophis</em> spp.), king snakes and milk snakes (<em>Lampropeltis</em> spp.)</td>
<td>Largest family of snakes; most are considered harmless to humans; a few species are dangerously toxic (e.g., African boomslang [<em>Dispholidus typus</em>])</td>
</tr>
<tr>
<td>Boidae</td>
<td>None</td>
<td>Most parts of the world</td>
<td><em>Boa</em> species, <em>Python</em> species</td>
<td>Constrictors; unsupervised children should not be allowed access to large constrictors</td>
</tr>
<tr>
<td>Viperidae</td>
<td>All</td>
<td>Americas, Asia</td>
<td>Rattlesnakes (<em>Crotalus</em> and <em>Sistrurus</em> spp.), cottonmouths and copperheads (<em>Agkistrodon</em> spp.), Lancehead pit vipers (<em>Bothrops</em> spp.)</td>
<td>Heat-sensing “pit” between each eye and nostril</td>
</tr>
<tr>
<td>Subfamily Crotalinae (pit vipers)</td>
<td>All</td>
<td>Americas, Asia</td>
<td>Rattlesnakes (<em>Crotalus</em> and <em>Sistrurus</em> spp.), cottonmouths and copperheads (<em>Agkistrodon</em> spp.), Lancehead pit vipers (<em>Bothrops</em> spp.)</td>
<td>Heat-sensing “pit” between each eye and nostril</td>
</tr>
<tr>
<td>Subfamily Viperinae (true vipers)</td>
<td>All</td>
<td>Europe, Africa, Middle East, Asia</td>
<td>Puff adder (<em>Bitis arietans</em>), Gaboon viper (<em>Bitis gabonica</em>)</td>
<td>No heat-sensing pits</td>
</tr>
<tr>
<td>Elapidae</td>
<td>All</td>
<td>Americas, Africa, Middle East, Asia</td>
<td>Cobras (<em>Naja</em> spp.), mambas (<em>Dendroaspis</em> spp.), kraits (<em>Bungarus</em> spp.), coral snakes (<em>Micrurus</em> spp.), and the venomous snakes of Australia</td>
<td>Highly variable venom effects—some largely neurotoxic, others causing severe local tissue damage</td>
</tr>
<tr>
<td>Hydrophiidae</td>
<td>All</td>
<td>Warm waters of the Pacific Ocean, Indian Ocean, and Oceana (none in the Atlantic Ocean)</td>
<td>Sea snakes including the pelagic sea snake (<em>Pelamis platurus</em>)</td>
<td>Neurotoxins and myotoxins; rarely bite humans unless provoked</td>
</tr>
</tbody>
</table>
analysis including total creatine kinase. A blood sample should be sent for typing and screening, although blood products are rarely actually required in management of snake bite. Samples collected later in the clinical course may be hard to cross match because venom and AV can interfere with the testing. Tourniquets placed in the field by laypeople should be cautiously removed after venous access is obtained, to watch for and treat adverse effects that may follow a sudden bolus of acidic, hyperkalemic blood mixed with venom into the systemic circulation. The bitten extremity should be marked at 2 or more sites proximal to the bite, and the circumferences at these locations should be assessed every 15 min to monitor for progressive edema—indicative of ongoing venom effects. Occasionally, the sharp, recurved teeth of snakes, including nonvenomous snakes, are left behind in wounds; they should be identified (using soft tissue radiographs or ultrasound as needed) and removed.

Assessing the severity of the envenomation in the field and at the hospital is essential (Table 725-2).

AVs are relatively specific for the snake species against which they are designed to protect. There is no benefit to administering an AV for an unrelated species, and doing so certainly involves unacceptable risk (e.g., anaphylaxis) and expense. If it is determined that the child requires AV, a search for the appropriate product should begin as soon as possible—checking the hospital pharmacy, regional poison control center, and perhaps local zoos and museums that keep captive snakes.

Table 725-3 lists the indications for administering AV.

In October 2000, Crotalidae polyvalent immune Fab known as CroFab was approved by the FDA for use in crotaline envenomations. CroFab is derived from sheep (ovine) antibodies and replaces the previously used AV derived from horses (equine-derived AV). The most important advantage of this AV is fewer hypersensitivity reactions, including both immediate and delayed reactions. A metaanalysis showed only 8% immediate hypersensitivity reactions and 13% delayed or serum sickness reactions after administration of CroFab, compared to an estimated 23-56% from the previous equine-derived AV.

CroFab is derived from 4 snakes, 3 from the genera Crotalus (the eastern diamondback rattlesnake, the western diamondback rattle- snake, and the Mohave rattlesnake) and 1 from the genera Agkistrodon (the cottonmouth water moccasin). It is effective against the venoms of all pit vipers in the United States. There is controversy regarding the use of CroFab in bites from copperheads (Agkistrodon contortrix) because they tend to cause fewer systemic effects. Most copperhead envenomations cause only local tissue swelling, ecchymosis, and pain, and generally do well even without AV. Serious envenomations, including fatalities, have followed copperhead bites, and any child with evidence of systemic toxicity should receive CroFab.

The half-life of CroFab is considerably shorter than that of crotaline venom constituents, and redosing is frequently needed to prevent or treat recurrence of venom effects. Patients with significant envenomation should be followed for late hematologic abnormalities (coagulopathy) that can occur up to 2 weeks after the bite. Although these

<table>
<thead>
<tr>
<th>Table 725-3</th>
<th>Indications for Snake Antivenom Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of systemic toxicity:</td>
<td>Hypotension, respiratory distress instability</td>
</tr>
<tr>
<td>Hemodynamic or respiratory</td>
<td></td>
</tr>
<tr>
<td>instability</td>
<td></td>
</tr>
<tr>
<td>Hemotoxicity</td>
<td>Clinically significant bleeding or abnormal coagulation studies</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Any evidence of toxicity: usually beginning with cranial nerve abnormalities and progressing to descending paralysis including the diaphragm</td>
</tr>
<tr>
<td>Evidence of worsening local toxicity</td>
<td>Progressive soft tissue swelling</td>
</tr>
</tbody>
</table>

![Figure 725-2 Southern Pacific rattlesnake bite (Crotalus oreganus helleri) in a 2 yr old boy. Note the fang marks, swelling, and bruising of the tissues (photograph taken 2 hr following the bite). (Courtesy of Sean Bush, MD.)](image)

**Table 725-2** Crotaline Envenomation: Determining the Degree of Envenomation

<table>
<thead>
<tr>
<th>DEGREE OF ENVENOMATION</th>
<th>CONTIGUOUS MANIFESTATIONS</th>
<th>SYSTEMIC MANIFESTATIONS</th>
<th>LABORATORY ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or trivial (&quot;dry bite&quot;)</td>
<td>Punctures or abrasions; pain and tenderness at bite</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mild or minimal</td>
<td>Punctures or abrasions; pain, tenderness, edema, and erythema at and adjacent to bite</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>Punctures or abrasions; pain, tenderness, edema, and erythema beyond area adjacent to bite</td>
<td>Perioral paresthesias; peripheral paresthesias; gustatory changes; nausea; emesis; diarrhea; weakness; light-headedness; diaphoresis; chills</td>
<td>↑PT; ↑PTT; ↓platelets; ↓ fibrinogen; ↑Thromboglobulin</td>
</tr>
<tr>
<td>Severe</td>
<td>Punctures or abrasions; pain, tenderness, edema, and erythema of entire extremity</td>
<td>Ventilatory insufficiency; hypotension; shock; bleeding; altered mental status; fasciculations; seizures</td>
<td>↑↑PT; ↑↑PTT; ↓↓platelets; ↓↓ fibrinogen; ↑↑Thromboglobulin</td>
</tr>
</tbody>
</table>

↑, increased; ↑↑, very increased; ↓, decreased; ↓↓, very decreased; PT, prothrombin time; PTT, partial thromboplastin time.

tend to be mild laboratory coagulopathies without clinical bleeding, rare cases of intracranial bleeding have been reported. Further AV therapy should be considered for such delayed onset or recurrent coagulopathy as outlined in Table 725-4.

**Disposition**

Any child with a potential venomous snake bite should be admitted to a closely observed setting for at least 24 hr, regardless of whether evidence of envenomation exists or AV has been given. Children with evidence of systemic toxicity should initially be admitted to an intensive care setting until stabilized.

**SPIDER BITES**

More than 20,000 venomous spiders have been identified, but most lack either potent venom or fangs long enough to penetrate human skin, and are therefore of no medical significance. No spiders can be considered truly deadly, meaning that an untreated bite in a human would be expected to cause death. The spiders of medical significance can be broadly divided into 2 major groups: those that cause a neurotoxic syndrome and those that cause tissue necrosis. In the United States, the only significant morbidities are caused by 1 genus of spider from each group: *Latrodectus* (the widow spiders) and *Loxosceles* (the fiddleback or recluse spiders).

**Neurotoxic Spiders**

The major neurotoxic spiders are the widow spiders (*Latrodectus* spp.), the funnel web spiders (*Atrax* and *Hydromyche* spp.—found in Australia), and the banana spiders (*Phoneutria* spp.—indigenous to Latin America).

**Venoms and Effects**

Neurotoxic spiders all possess venoms that act at neural synapses, both at neuromuscular junctions and at autonomic nervous system junctions. All of the widow spiders (*Latrodectus* spp., including the well-studied black widow [*Latrodectus mactans*; Fig. 725-3]) and the Australian red-back spider [*Latrodectus hasselti*]) possess very similar venoms, with the most important neurotoxin being α-latrotoxin. The neurotoxin of the Sydney funnel web spider (*Atrax robustus*) is robustoxin.

Bites by the neurotoxic spiders tend to be very painful, and the offending spider is often seen. Systemic effects may include hypertension, tachycardia, bradycardia, hypersalivation, diaphoresis, and diffuse muscle spasms.

**Management**

Management of neurotoxic spider envenomation centers on sound supportive care. Several *Latrodectus* AVs are available, and each appears to be effective regardless of which species of widow spider was responsible for the bite. There is also an AV for the Sydney funnel web spider, the only species of funnel web that has caused human fatalities (none since the introduction of the AV), and a polyspecific AV for the banana spider in South America. These AVs should be used in significant bites with potentially serious systemic effects. The package insert for the appropriate product is used to guide therapy.

In the United States, *Latrodectus* AV is administered to reverse serious systemic effects of widow spider envenomation. One vial is given either intramuscularly (IM) or IV. Efficacy is usually noted within 1 hr of administration, reversal of systemic toxicity and relief of pain being noted. Occasionally, a second vial is necessary. There have been deaths related to acute nonallergic anaphylactic reactions to the U.S. AV, so its administration should be undertaken with due caution and close monitoring.

If AV is to be withheld or is not available, generous doses of opioid analgesics and benzodiazepines may be used to ease symptoms (although this may require up to 72 hr of therapy).

**Disposition**

Most neurotoxic spider bite victims, even those requiring AV, can be discharged from the emergency department if they have a satisfactory response to therapy. Parents should be warned to bring their child back for any reoccurrence of venom effects. Children with more-severe cases should be admitted for 24 hr of monitoring.

**Necrotizing Spiders**

**Venoms and Effects**

Although many spiders may cause a small amount of local tissue damage after their bites, the spiders most notorious for their dermonecrotic potential are the violin or recluse spiders of the genus *Loxosceles*. The best known member of this genus is the brown recluse (*Loxosceles reclusa*; Fig. 725-4), found in the midwestern and southern portions of the United States. The venom of *Loxosceles* spiders contains a phospholipase enzyme, sphingomyelinase D, which attacks cell membranes and can cause local tissue damage that can occasionally be severe. The bite of this spider, most common between April and October, is generally painless and initially goes unnoticed. A few hours after the bite, pain related to focal ischemia begins at the site. Within a day, the site may have a central clear or blood-filled vesicle with surrounding ecchymosis and a rim of pale ischemia. The lesion may gradually expand over a period of days to weeks until necrotic tissue sloughs and healing begins (Fig. 725-5).

Rare cases of systemic loxoscelism appear to be more common in young children than adults. Patients present with systemic toxicity, including fever, chills, nausea, malaise, diffuse macular rash, and petechiae, and may experience hemolysis, coagulopathy, and/or renal failure.

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**Table 725-4** Indications for Administration of Additional Antivenom in Patients with Recurrent Coagulopathy or Thrombocytopenia After Initial Control

- Evidence of clinically significant bleeding
- Platelet count below 25,000/cu mm
- International normalized ratio (INR) greater than 3
- Activated partial thromboplastin time (aPTT) greater than 50 sec
- Fibrinogen less than 50 mg/dL
- Presence of multicomponent coagulopathy
- Worsening trend in a patient with prior severe coagulopathy
- High-risk behavior for trauma
- Certain comorbid conditions (e.g., systemic vasculitis, seizure disorders, prior stroke)


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**Note**

For the purposes of this chapter, the brown recluse spider is considered a necrotizing spider. Although less common in the United States, the red hourglass-shaped spider of South America is a true neurotoxic spider.
In cases of suspected necrotic arachnidism, when no spider was actually seen by the patient, a broad differential diagnosis must be considered to ensure appropriate management of the true etiology. The differential diagnosis includes skin infections (particularly methicillin-resistant *Staphylococcus aureus*; see Chapter 181), bites by other arthropods (e.g., fleas, ticks), pyoderma gangrenosum, or ecthyma gangrenosum.

**Management**

For necrotizing spider bites, management of the wound involves sound supportive care, including intermittent local ice therapy for the 1st 72 hr and administration of antibiotics if there is any question of secondary bacterial infection. Daily wound cleansings, combined with splinting of the bitten area, should be performed until the wound is healed.

Nothing has been definitively proven effective in limiting the extent of necrosis following a spider bite. There is no role for steroids in managing necrotic arachnidism. Dapsone, although used anecdotally in managing *Loxosceles* bites in adults, is not approved for use in children and should not be prescribed.

Children appearing systemically unwell should be admitted and undergo laboratory evaluation (complete blood count, coagulation studies, and urinalysis). Systemic loxoscelism is managed with intravenous hydration, management of renal failure as needed, and a brief course of systemic steroids to stabilize red blood cell membranes. Although there are documented fatalities following bites by the South American violin spider (*Loxosceles laeta*), there has never been a definitively proven fatality following a brown recluse bite in the United States. No AV is commercially available in the United States for management of necrotizing spider bites such as those from *Loxosceles* species.

**Disposition**

Victims with potentially necrotic bites should be monitored for a few days with daily wound checks. Local, intermittent cooling therapy should be continued for approximately 72 hr. Any child with a probable necrotizing spider bite and evidence of systemic involvement should be admitted to be watched for hemolysis and coagulopathy.

**SCORPION STINGS**

Of the more than 1,200 species of scorpions worldwide, only a few cause more than a painful sting. In the United States, there is 1 medically significant scorpion, the bark scorpion (*Centruroides sculpturatus* [formerly *Centruroides exilicauda*]). Although this scorpion has caused death in children in the past, such an outcome is exceedingly rare. It is found only in Arizona and small areas of immediately surrounding states. In other regions of the world, especially Latin America, Africa, the Middle East, and Asia, a number of scorpions regularly cause fatalities, particularly in small children.

![Figure 725-4 Male recluse spider (*Loxosceles* spp.). Note the distinct violin-shaped marking on the dorsum of the cephalothorax. (Courtesy of Michael Cardwell/Extreme Wildlife Photography.)](image1)

![Figure 725-5 Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt. Ulceration and necrosis at day 1 (A), day 9 (B), day 16 (C), and day 25 (D). (From Isbister G, Fan HW: Spider bite. Lancet 378:2039–2046, 2011, Fig. 3. Photographs by Ceila MS Malaque.)](image2)
Venoms and Effects
The major components of important scorpion venoms are neurotoxins that alter neural membrane ionic channels, causing autonomic and cardiovascular dysfunction through the release of acetylcholine and catecholamines. Manifestations of scorpion stings in children vary from mild to severe and may include pain, paresthesias, roving eye movements, cranial nerve dysfunction, opisthotonos/emprostonhotos, seizures, hypertensive crisis, cardiovascular collapse, and respiratory failure. Two important ingestions that can be confused with a bark scorpion envenomation are organophosphate poisoning (see Chapter 63) and methamphetamine intoxication (see Chapter 114). The opsonolus-like roving eye movements seen in bark scorpion envenomations are not seen in the above ingestions and may help differentiate these conditions.

Management
Most stings require only pain control and respond well to ice, immobilization, and analgesics. Management of severe stings should begin with the ABCs. Opioid analgesics may have some synergy with scorpion neurotoxins and should be used with caution. Benzodiazepines may be more useful, especially for severe muscle spasms or sedation of the agitated child. Approximately 20 different scorpion AVs are available worldwide, but their use is controversial because of variable efficacy and the risk of potential nonallergic anaphylaxis. Practitioners should be familiar with the local standard of care for treating the stings of their indigenous scorpions and should consult a local or regional expert for assistance as necessary. In August 2011, the FDA approved a bark scorpion–specific AV, Anascorp, for use in the United States. It is manufactured in Mexico and marketed there under the name Alacaramy. The AV is generally given to any patient with cranial nerve or somatic skeletal neuromuscular dysfunction. The starting dose is 3 vials given IV, followed by another vial if symptoms still persist 30-60 min later and up to 5 vials were used in the initial study. Anascorp is currently only approved for IV administration; however, there are case reports of it being given IM and IO in children without IV access. For more specific information about the administration of Anascorp, the practitioner should contact the Arizona Poison and Drug Information Center for details and assistance (800-222-1222). In some regions of the world, prazosin is used in severe scorpion stings to ameliorate acute cardiovascular effects.

Disposition
The child with evidence of systemic toxicity following a scorpion sting should be admitted for at least 24 hr of monitoring (including cardiac monitoring) and, if envenomation is severe, should be monitored in a pediatric intensive care unit. In the absence of systemic toxicity and with adequate pain control, children >1 yr can be discharged to go home with a responsible adult.

HYMENOPTERA STINGS
The insect order Hymenoptera includes the stinging ants, bees, and wasps, which are characterized by the presence of a modified ovipositor (the “sting” or “stinger”) at the end of the abdomen through which venom is injected. Various members of the order can be found throughout the world.

Venoms and Effects
Hymenoptera venoms, mixtures of proteins and vasoactive substances, are not very potent. Most stings result in only local pain, redness, and swelling, followed by itching and resolution. Some patients experience a large local reaction in which swelling progresses beyond the sting site, possibly involving the entire extremity. Approximately 0.4-0.8% of children are at risk for acute, life-threatening allergic reactions as a result of hymenoptera venom sensitivity. Each year, an estimated 50-150 people in the United States die of allergic anaphylaxis caused by hymenoptera stings (see Chapter 70). Rare cases of delayed serum sickness can follow hymenoptera stings (see Chapter 150). Finally, with the spread of Africanized honey bees (Apis mellifera scutellata), massive stinging episodes resulting in systemic venom toxicity (hypotension, respiratory failure, shock, hemolysis, and renal failure) appear to be increasing in Latin America and the southwestern U.S. states.

Management
Children with typical local reactions can be treated with application of cold compresses and with analgesics and antihistamines as needed. Children with large local reactions should also receive a 5 day course of oral corticosteroids and a prescription for an epinephrine autoinjection kit (and instructions in its use) prior to discharge. Patients presenting with urticaria, angioedema, wheezing, or hypotension should be treated aggressively for an immediate hypersensitivity reaction with intramuscular epinephrine (0.01 mg/kg, up to 0.3-0.5 mg of 1 : 1,000 formulation), airway management as needed, oxygen, intravenous fluids, antihistamines, and corticosteroids. Children suffering massive stinging episodes should undergo treatment similar to that for allergic anaphylaxis.

Disposition
Children with local reactions (limited or large local) can be discharged with continued care as outlined previously and instructions for wound precautions. More difficult disposition decisions are involved for children with systemic manifestations. Children with only diffuse urticaria, who are stable after a period of observation, can be discharged in the care of a responsible adult to continue antihistamines and steroids and to carry an epinephrine self-administration kit. These children seem to be at little risk for progressing to systemic anaphylaxis with future stings. Children suffering more than simple hives (e.g., wheezing, evidence of laryngeal edema or cardiovascular instability) should be admitted for 24 hr of observation and should receive a referral to an allergist for testing for hymenoptera venom sensitivity and possible immunotherapy. Immunotherapy reduces the risk of systemic anaphylaxis from future stings in high-risk patients from somewhere between 30% and 60% to less than 5%.

MARINE ENVENOMATION
The most commonly encountered venomous marine creatures are the jellyfish (Cnidaria), stingrays (Chondrichthyes), and members of the family Scorpaenidae—the lionfish, scorpionfish, and stonefish. Although most injuries occur when a child ventures into the animal’s natural environment, lionfish (Pterois spp.) are commonly kept in private aquariums and children may be stung if they attempt to handle these beautiful fish.

Venoms and Effects
All jellyfish have unique stinging cells called nematocysts. These cells contain a highly folded tubule that everts on contact and injects venom. The venom is antigenic and can be dermonecrotic, hemolytic, cardio- toxic, or neuropathic, depending on the species. The nematocysts can sting even after the tentacle is severed from the body and after the jellyfish is dead. The Pacific box jellyfish (Chironex fleckeri) of Australia, with its cardiotoxic venom, is known to cause rapidly fatal stings. Although fatal anaphylaxis to jellyfish stings has been reported in coastal waters of the United States, these events are rare. For clinicians in the Americas, the primary concern with jellyfish stings is localized pain that may be associated with paresthesias or pruritus. Rarely, jellyfish victims may have systemic symptoms such as nausea, vomiting, headache, and chills.

Stingrays have a sharp, retroserrated spine and associated venom gland at the base of the tail. Stings tend to occur when the victim steps on the animal hidden in the surf. Injuries involve jagged lacerations from the spine, often with retained debris (spine fragments, glandular tissue, sand, etc.), and the venom has vasoconstrictive properties that can result in tissue necrosis and poor wound healing. Stingray envenomations are noteworthy for immediate and intense pain at the site of injury that lasts 24-48 hr. Some patients experience nausea, vomiting, and muscle cramps, and, rarely, hypotension or seizures.

The Scorpaenidae have venomous dorsal, pelvic, and anal spines that become erect when threatened. The glands associated with these spines contain venoms that result in direct myotoxicity leading to...
paralysis of cardiac, involuntary, and skeletal muscles. Envenomation causes immediate pain that may persist for hours or days. Victims may experience intense local tissue destruction in which superinfections are common. Systemic symptoms include vomiting, abdominal pain, headache, delirium, seizures, and respiratory failure.

Management
Treatment of jellyfish stings begins in the ocean. The involved skin should be quickly rinsed in seawater (fresh water may stimulate further nematocyst firing). Dousing the sting site with vinegar or rubbing alcohol can inhibit nematocyst discharge. Visible tentacle fragments should be removed with a gloved hand or forceps, and microscopic fragments may be removed by gently shaving the affected area. Folk remedies such as rubbing the sting with sand and applying urine are not helpful and cause more irritation. Meat tenderizer is not effective. Antihistamines and corticosteroids are indicated for swelling and urticaria. An apparent, acute allergic reaction should be treated with intramuscular epinephrine. Antibiotics are not needed.

Treatment of stingray and Scorpaenidae stings is similar. These toxins are heat labile, and immersion in hot water (approximately 42°C [107.6°F]) for 30-60 min denatures the protein constituents and decreases pain significantly. The wounds should be thoroughly cleaned and explored with use of local or regional anesthesia to rule out retention of spine or integument fragments. Stingray spines are radiopaque and may be seen on plain films of the wounded area or identified by ultrasonography. Lacerations should be treated with delayed primary closure or allowed to heal by secondary intention. Systemic analgesia should be provided as needed. Because of the risk of secondary bacterial infection, there should be a low threshold for administering prophylactic antibiotics to cover *Staphylococcus*, *Streptococcus*, and *Vibrio* species, and wounds should be rechecked daily for a few days.

Disposition
After wound care, most victims can be discharged home with responsible adults. If there are significant systemic effects after pain control is achieved, the child should be admitted for monitoring and further care as needed.

Bites and stings by venomous creatures are common occurrences in children, but they uncommonly cause major morbidity or mortality. The majority of such injuries do very well with sound supportive care. In serious cases, aggressive management of the ABCs combined with specific interventions (such as AVs when available) maximize the potential for an optimal outcome. A low threshold should be maintained for consulting specialists in envenomation medicine, available through regional poison control centers.

Bibliography is available at Expert Consult.
Bibliography


“Normal values” (reference intervals) are difficult to establish within the pediatric population. Differences in genetic composition, physiologic development, environmental influences, and subclinical disease are variables that need to be considered when developing reference intervals. Other considerations for further defining reference intervals include partitioning based on sex and age. The most commonly used reference range is generally given as the mean of the reference population ± 2 standard deviations (SD). This is acceptable when the distribution of results for the tested population is essentially gaussian. The serum sodium concentration in children, which is tightly controlled physiologically, has a distribution that is essentially gaussian; the mean value ± 2 SD gives a range very close to that actually observed in 95% of children (Table 726-1). However, not all analytes have a gaussian distribution. The serum creatine kinase level, which is subject to diverse influences and is not actively controlled, does not show a gaussian distribution, as evidenced by the lack of agreement between the range actually observed and that predicted by the mean value ± 2 SD. In these cases, a reference interval defining the 2.5-97.5 percentiles is typically used.

Reference cutoffs are typically established from large studies with a large reference population. Examples of these cutoffs are illustrated by reference cutoffs established for cholesterol, lipoproteins, and neonatal bilirubin. Patient results exceeding these cutoffs have a future risk of acquiring disease. A final modification needed for reporting reference intervals is referencing the Tanner stage of sexual maturation, which is most useful in assessing pituitary and gonadal function.

The establishment of common reference intervals remains an elusive goal. Although some patient results are directly comparable between laboratories and methods, most are not. Careful interpretation of patient results must consider when testing was performed and what method was used. Higher-order methods, methods that are more accurate and precise, continue to be slowly developed. These will be critical to the standardization of tests and the establishment of common reference intervals.

**ACCURACY AND PRECISION OF LABORATORY TESTS**

Technical accuracy, or trueness, is an important consideration in interpreting the results of a laboratory test. Because of improvements in methods of analysis and elimination of analytic interference, the accuracy of most tests is limited primarily by their precision. Accuracy is a measure of the nearness of a test result to the actual value, whereas precision is a measure of the reproducibility of a result. No test can be more accurate than it is precise. Analysis of precision by repetitive measurements of a single sample gives rise to a gaussian distribution with a mean and an SD. The estimate of precision is the coefficient of variation (CV):

\[
CV = \frac{SD}{Mean} \times 100
\]

The CV is not likely to be constant over the full range of values obtained in clinical testing, but it is approximately 5% in the normal range. The CV is generally not reported, but it is always known by the laboratory. It is particularly important in assessing the significance of changes in laboratory results. For example, a common situation is the need to assess hepatotoxicity incurred as a result of the administration of a therapeutic drug and reflected in the serum alanine aminotransferase (ALT) value. If serum ALT increases from 25 units/L to 40 units/L, is the change significant? The CV for ALT is 7%. Using the value obtained ± 2 × CV to express the extremes of imprecision, it can be seen that a value of 25 units/L is unlikely to reflect an actual concentration of >29 units/L, and a value of 40 units/L is unlikely to reflect an actual concentration of <34 units/L. Therefore, the change in the value as obtained by testing is likely to reflect a real change in circulating ALT levels. Continued monitoring of serum ALT is indicated, even though both values for ALT are within normal limits. Likely in this case is only a probability. Inherent biologic variability is such that the results of 2 successive tests may suggest a trend that will disappear on further testing.

The precision of a test may also be indicated by providing confidence limits for a given result. Ordinarily, 95% confidence limits are used, indicating that it is 95% certain that the value obtained lies between the 2 limits reported. Confidence limits are calculated using the mean and SD of replicate determinations:

\[
95\% \text{ confidence limits} = \text{Mean} \pm t \times \text{SD}
\]

where \( t \) is a constant derived from the number of replications. In most cases, \( t = 2 \).

Accuracy is expressed by determining the difference, or bias, between results from a comparative method and a definitive or reference method. A definitive or reference method provides results with increased precision and accuracy compared to the clinical laboratory. When these methods are used, along with highly purified materials (i.e., Standard Reference Materials from the National Institute of Standards and Technology) to establish values for assay calibrators used in the clinical laboratory, the accuracy of patient results is improved. Creatinine, hemoglobin A1c, and neonatal bilirubin are examples in which the accuracy of these tests has been improved.

**SENSITIVITY, ACCURACY, AND ANALYTIC TESTING**

In some circumstances, the sensitivity and accuracy of an analysis are reduced or increased as functions of clinical purpose. For example, ion exchange chromatography of plasma amino acids for the diagnosis of inborn errors of metabolism is usually performed at an analytic sensitivity that allows measurement of all of the amino acids with a single set of standards. The range of values is approximately 20-800 µmol/L, and accuracy is poor at values ≤20 µmol/L. The detection of homocysteine in this type of analysis suggests an inborn error of methionine metabolism. If the analysis is adjusted to achieve greater analytic sensitivity, it is possible to measure homocysteine accurately in normal plasma (3-12 µmol/L). This more sensitive test is used to assess cobalamin status and analyze risk factors for atherosclerotic cardiovascular disease.

**PREDICTIVE VALUE OF LABORATORY TESTS**

Predictive value (PV) theory deals with the usefulness of tests as defined by their clinical sensitivity (ability to detect a disease) and specificity (ability to define the absence of a disease).
The problems addressed by PV theory are false-negative and false-positive test results. Both are major considerations in interpreting the results of screening tests in general and neonatal screening tests in particular.

Testing for HIV seroreactivity illustrates some of these considerations. If it is assumed that approximately 1,100,000 of 284,000,000 residents of the United States are infected with HIV (prevalence = 0.39%) and that 90% of those infected demonstrate antibodies to HIV, then we can consider the usefulness of a simple test with 99% sensitivity and 99.5% specificity (see Chapter 276). If the entire population of the United States were screened, it would be possible to identify most of those infected with HIV.

\[ 1,100,000 \times 0.9 \times 0.99 = 980,100 \times 0.891 \]

However, there will be 119,900 false-negative test results. Even with 99.5% specificity, the number of false-negative or false-positive test results would be larger than the number of true-positive results:

\[ 284,000,000 \times 0.0005 = 1,420,000 \]

In addition, there will be 281,480,000 true-negative results:

\[ \text{PV of positive test result} = \frac{980,100}{(980,100 + 1,420,000)} \times 100 = 41\% \]

\[ \text{PV of negative test result} = \frac{281,480,000}{(281,480,000 + 119,900)} \times 100 = 99.96\% \]

Given the high cost associated with follow-up and the anguish produced by a false-positive result, it is easy to see why universal screening for HIV seropositivity received a low priority immediately after the introduction of testing for HIV infection.

By contrast, we can consider the screening of 100,000 individuals from groups at increased risk for HIV in whom the overall prevalence of disease is 10%, with all other considerations being unchanged.

\[ \text{True-positive results} = 0.9 \times 0.99 \times 10,000 = 8,910 \]

\[ \text{False-positive results} = 0.005 \times 90,000 = 450 \]

\[ \text{False-negative results} = 10,000 - 8,910 = 1,090 \]

\[ \text{PV of positive test result} = \frac{8,910}{8,910 + 450} \times 100 = 95\% \]

\[ \text{PV of negative test result} = \frac{89,500}{89,550 + 1,090} \times 100 = 99\% \]

These 2 hypothetical testing strategies show that the diagnostic efficiency of testing depends heavily on the prevalence of the disease being tested for, even with a superior test, such as the test for HIV antibodies. Because the treatment of pregnant women infected with HIV is effective in preventing vertical transmission of the infection, screening has now been expanded to all pregnant women. The proven effectiveness of current therapy in preventing neonatal infection has intensified screening for HIV early in pregnancy.

However, because of the long time needed to test for HIV antibodies, it was difficult to screen women during labor and provide the necessary therapy. Recently, rapid HIV antibody testing procedures using a fingerstick or venipuncture to obtain whole blood, plasma, or serum, and tests using oral fluid were approved (Table 276-2). The HIV test results are usually obtained in <20 min. The collection of oral fluid samples provides an alternative for individuals who avoid HIV testing because of the dislike of needlesticks. HIV testing using whole blood or oral fluid is classified as a waived test under the Clinical Laboratory Improvement Amendments of 1988, and these tests are allowed in a point-of-care setting. Waived tests are simple laboratory procedures that use methodologies that are so simple and accurate as to render the likelihood of an erroneous result by the user negligible. A positive rapid HIV test result is then confirmed by Western blot analysis or immunofluorescence assay.

According to the U.S. Centers for Disease Control and Prevention, 162 infants were born with HIV in 2010 in the United States. Rapid HIV testing during labor allows for implementation of antiretroviral therapy for HIV-infected women who have not been tested or are unaware of their HIV status. The initiation of therapy at the time of labor or within the 1st 12 hr of an infant’s birth significantly reduces the risk of mother-to-child transmission. In the mother–infant rapid intervention at delivery study, it was shown that the sensitivity and specificity of a rapid whole blood test for HIV during labor were 100% and 99.9%, respectively, with a positive PV of 99.6%. The median turnaround time for obtaining results from blood collection to patient notification was only 66 min. The performance of the rapid blood test was better than that of the standard HIV enzyme immunoassay, which had sensitivity and specificity of 100% and 99.8%, respectively, with a positive PV of 76%. In addition, the median turnaround time from blood collection to patient notification was 28 hr. As a result, rapid whole blood HIV testing is now the standard of care for women in labor with undocumented HIV status.

Rapid HIV testing can also be used in developing countries. In resource-poor settings, because of the lack of properly equipped laboratories, skilled technologists, and basic resources, such as electricity and water, these self-contained, point-of-care HIV tests are very attractive. In areas of Asia and Africa in which HIV is epidemic, screening pregnant women with rapid HIV tests and offering antiretroviral therapy can significantly reduce the transmission of HIV to hundreds of thousands of infants.

### NEONATAL SCREENING TESTS

Almost all of the diseases detected in neonatal screening programs have a very low prevalence, and for the most part, the tests are quantitative rather than qualitative. In general, the strategy is to use the initial screening test to separate a highly suspect group of patients from normal infants (i.e., to increase the prevalence) and then to follow this suspect group aggressively. There are 2 common strategies used to detect congenital hypothyroidism (see Chapter 568.2): 1 uses thyroid-stimulating hormone for the initial screen and the other uses thyroxine. In the thyroxine strategy for congenital hypothyroidism, which has a prevalence of 25 in 100,000 liveborn infants, the initial test performed is for thyroxine in whole blood. Infants with the lowest 10% of test results are considered suspect. If all infants with hypothyroidism were included in the suspect group, the prevalence of disease in this group would be 250 in 100,000 infants. The original samples obtained from the suspect group are retested for thyroxine and are tested for thyroid-stimulating hormone. This second round of testing results in an even more highly suspect group composed of 0.1% of the infants screened and having a prevalence of hypothyroidism of 25,000...
in 100,000 subjects. This final group is aggressively pursued for further testing and treatment. Even with a 1,000-fold increase in prevalence, 75% of the aggressively tested population is euthyroid. The justifications advanced for the program are that treatment is easy and effective and that the alternative, if congenital hypothyroidism is undetected and untreated—long-term custodial care—is both unsatisfactory and expensive.

At its inception, newborn screening was driven by the selection of genetic diseases whose clinical manifestations developed postnatally, such as phenylketonuria, galactosemia, and hypothyroidism. Diseases selected for screening typically had to meet certain criteria. The prevalence of disease had to meet a minimum, typically 1 in 100,000. Disease selection required demonstrated reduction in morbidity and mortality in the neonatal period. Effective therapies needed to be available, and the cost of screening and the feasibility of laboratory testing were also considerations in this selection process.

More common diseases have also become targets for neonatal screening programs. Sickle cell disease (see Chapter 462.1), easily detected using liquid chromatography or isoelectric focusing, can be treated more effectively if it is diagnosed before clinical signs appear. In addition, the results of neonatal screening for cystic fibrosis (CF; see Chapter 403) show that there are clear benefits associated with preclinical diagnosis, but also that there are some inherent difficulties associated with genetic screening for complex autosomal recessive diseases that are common and are caused by a rather large number of mutations (>1,500) of a single gene. The definitive diagnostic test for CF is the measurement of concentrations of chloride in sweat, a test that is not practical during the 1st wk of life. Neonates with CF generally have elevations in whole blood trypsinogen. This test allows the identification of a group of neonates at risk for CF. Unfortunately, trypsinogen as an initial screening test has a high false-positive rate, an unfavorable characteristic that creates unnecessary anxiety among newborn parents and families, and is costly because of the time and expense for medical follow-up. Performing DNA analysis for common mutations that cause CF reduces the size of the suspect group and identifies neonates with a higher likelihood of disease. This 2-tiered strategy identifies a manageable number of infants on whom to perform sweat tests. Problems include the following: (1) Uncommon mutations are not included in the screening panel (thus, cases of CF caused by these mutations can be missed); (2) common mutations that cause clinically innocent elevations of whole blood trypsinogen in heterozygous neonates cause potentially alarming false-positive findings; and (3) CF in patients with normal sweat test results is rare but is likely to be missed.

Tandem mass spectrometry (MS/MS) is a technically advanced method in which many compounds are initially fragmented and separated by molecular weight. Each compound is then fragmented again. Identification of compounds is based upon characteristic fragments. The process requires roughly 2 min per sample and can detect 20 or more inborn errors of metabolism. The effects of prematurity, neonatal illness, and intensive neonatal management on metabolites in blood complicate the interpretation of results. The PV of a positive screening result is likely to be <10%; that is, 90% of positive results are not indicative of a genetic disorder of metabolism. Nonetheless, MS/MS permits a diagnosis to be made before clinical illness develops and has revolutionized the purpose and ability of newborn screening. MS/MS is not directed toward diseases defined as treatable, but it is directed toward all of the diseases, each of which is rare, that the technique can identify.

Electrospray MS/MS permits the detection of rare inborn errors of metabolism and has been introduced as a newborn screening tool all around the world. Since 1998, when mass spectrometry was implemented in Australia, the rate of detection per 100,000 births has been 15.7, significantly higher than the rate of 8.6-9.5 in the 6 preceding 4 yr periods. Disorders of fatty acid oxidation, particularly medium-chain acyl coenzyme A dehydrogenase deficiency (see Chapter 86), accounted for the majority of increased diagnoses.
The use of laboratory tests in refining a differential diagnosis satisfies PV theory because a correct differential diagnosis should result in a relatively high prevalence of the disease under consideration. An example of testing in refining a differential diagnosis is the measurement of urinary vanillylmandelic acid (VMA) for the diagnosis of neuroblastoma (see Chapter 498). A simple spot test for VMA is not useful in general screening programs because of the low prevalence of neuroblastoma (3 cases/100,000) and the low sensitivity of the test (69%). Even though the specificity of urinary VMA is 99.6%, testing of 100,000 children would produce 2 true-positive test results, 400 false-positive results, and 1 false-negative result. The PV of a positive result in this setting is 0.5%, and the PV of a negative result is 99.99%, not much different from the assumption that neuroblastoma is not present. Testing for urinary VMA in a 3 yr old child with an abdominal mass, however, gives a useful result because the prevalence of neuroblastoma is at least 50% in 3 yr old children with abdominal masses. If 100 such children are tested and the prevalence of neuroblastoma in the group is assumed to be 50%, then a satisfactory PV is obtained.

$$\text{PV of positive test result} = \frac{0.69 \times 50}{0.69 \times 50 + (0.004 \times 50)} \times 100 = 99\%$$

$$\text{PV of negative test result} = \frac{0.996 \times 50}{0.996 \times 50 + (0.31 \times 50)} \times 100 = 76\%$$

Thus, in this situation, a test with low sensitivity is powerful in refining the differential diagnosis because the PV of a positive result is almost 100% in the setting of high prevalence.

**Serologic Testing**

Using laboratory testing to refine a differential diagnosis poses problems, as exemplified by serologic testing for Lyme disease, which is a tick-borne infection by *Borrelia burgdorferi* that has various manifestations in both early and late stages of infection (see Chapter 222). Direct demonstration of the organism is difficult, and serologic test results for Lyme disease are not reliably positive in young patients presenting early with erythema chronicum migrans. These results become positive after a few weeks of infection and remain positive for a number of years. In an older population being evaluated for late-stage Lyme disease, some individuals will have recovered from either clinical or subclinical Lyme disease and some will have active Lyme disease, with both groups having true-positive serologic test results. Of individuals without Lyme disease, some will have true-negative serologic test results, but a significant percentage will have antibodies to other organisms that cross react with *B. burgdorferi* antigens.

This set of circumstances gives rise to a number of problems. First, the protean nature of Lyme disease makes it difficult to ensure a high prevalence of disease in subjects to be tested. Second, the most appropriate antibodies to be detected are imperfectly defined, leading to a wide variety of tests with varying false-positive and false-negative rates. Third, the natural history of the antibody response to infection and the difficulty of showing the causative organism directly combine to make laboratory diagnosis of early Lyme disease difficult. Fourth, in the diagnosis of late-stage Lyme disease in older subjects, the laboratory diagnosis is plagued by misleading positive (either false-positive or true-positive, but not clinically relevant) results, typically an enzyme-linked immunosorbent assay that uses whole *B. burgdorferi* organisms. In a review of 788 patients referred to a specialty clinic with the diagnosis of Lyme disease, the diagnosis was correct in 180 patients, 156 patients had true seropositivity without active Lyme disease, and 452 had never had Lyme disease, even though 45% of them were found to be seropositive by at least 1 test before referral.

A 2-step approach, similar to that used in HIV testing, is commonly used: a screening test that has high sensitivity (e.g., enzyme-linked immunosorbent assay) and excellent negative PV, followed by a very specific confirmatory test for verification of positive screening test results (e.g., Western blot to detect antibodies to selected bacterial antigens). Negative screening test results and negative verification test results are reported as negative. Positive verification test results are reported as positive. However, standardization of the testing procedures is difficult in North America, where only 1 pathogenic strain of *B. burgdorferi* is found, and more difficult elsewhere in the Northern hemisphere, where as many as 3 pathogenic strains are present. Identification of microbial DNA in body fluids by polymerase chain reaction is definitive but invasive.
Laboratory Screening
Screening profiles (Table 726-4) are used as part of a complete review of systems, to establish a baseline value, or to facilitate patient care in specific circumstances, such as (1) when a patient clearly has an illness, but a specific diagnosis remains elusive; (2) when a patient requires intensive care; (3) for postmarketing surveillance and evaluation of a new drug; and (4) when a drug is used that is known to have systemic adverse effects. Laboratory screening tests should be used in a targeted manner to supplement, not supplant, a complete history and physical examination.

ACKNOWLEDGMENTS
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Bibliography is available at Expert Consult.
Bibliography


Chapter 727
Reference Intervals for Laboratory Tests and Procedures
Stanley F. Lo

In Tables 727-1 through 727-5, the reference intervals apply to infants, children, and adolescents when possible. For many analyses, separate reference intervals for children and adolescents are not well delineated. When interpreting a test result, the reference interval supplied by the laboratory performing the test should always be used as these intervals are instrument and/or method dependent. Figures 727-1 and 727-2 provide estimations related to dosages. Figure 727-3 is a nomogram for risk assessment of hyperbilirubinemia.

Bibliography is available at Expert Consult.

Table 727-1
Prefixes Denoting Decimal Factors in Table 727-5

<table>
<thead>
<tr>
<th>PREFIX</th>
<th>SYMBOL</th>
<th>FACTOR</th>
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</thead>
<tbody>
<tr>
<td>Mega-</td>
<td>M</td>
<td>10^6</td>
</tr>
<tr>
<td>Kilo-</td>
<td>k</td>
<td>10^3</td>
</tr>
<tr>
<td>Hecto-</td>
<td>h</td>
<td>10^2</td>
</tr>
<tr>
<td>Deka-</td>
<td>da</td>
<td>10^1</td>
</tr>
<tr>
<td>Deci-</td>
<td>d</td>
<td>10^-1</td>
</tr>
<tr>
<td>Centi-</td>
<td>c</td>
<td>10^-2</td>
</tr>
<tr>
<td>Milli-</td>
<td>m</td>
<td>10^-3</td>
</tr>
<tr>
<td>Micro-</td>
<td>µ</td>
<td>10^-6</td>
</tr>
<tr>
<td>Nano-</td>
<td>n</td>
<td>10^-9</td>
</tr>
<tr>
<td>Pico-</td>
<td>p</td>
<td>10^-12</td>
</tr>
<tr>
<td>Femto-</td>
<td>f</td>
<td>10^-15</td>
</tr>
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Table 727-2
Abbreviations Used in Table 727-5

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab</td>
<td>Absorbance</td>
</tr>
<tr>
<td>AU</td>
<td>Arbitrary unit</td>
</tr>
<tr>
<td>BB</td>
<td>Brain isoenzyme of creatine kinase</td>
</tr>
<tr>
<td>cap</td>
<td>Capillary</td>
</tr>
<tr>
<td>CH50</td>
<td>Dilution required to lyse 50% of red blood cells; indicates complement activity</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatinine</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>F</td>
<td>Female</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>HbCO</td>
<td>Carboxyhemoglobin</td>
</tr>
<tr>
<td>hpf</td>
<td>High-power field</td>
</tr>
<tr>
<td>hr</td>
<td>Hour, hours</td>
</tr>
<tr>
<td>IU</td>
<td>International unit of hormone activity</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>M</td>
<td>Male</td>
</tr>
<tr>
<td>MB</td>
<td>Heart isoenzyme of creatine kinase</td>
</tr>
<tr>
<td>mEq/L</td>
<td>Milliequivalents per liter</td>
</tr>
<tr>
<td>min</td>
<td>Minute, minutes</td>
</tr>
<tr>
<td>mm^3</td>
<td>Cubic millimeter, microliter (µL)</td>
</tr>
<tr>
<td>mm Hg</td>
<td>Millimeters of mercury</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>mo</td>
<td>Month, months</td>
</tr>
<tr>
<td>mol</td>
<td>Mole</td>
</tr>
<tr>
<td>mOsm</td>
<td>Milliosmole</td>
</tr>
<tr>
<td>MW</td>
<td>Relative molecular weight</td>
</tr>
<tr>
<td>ND</td>
<td>Not detected</td>
</tr>
<tr>
<td>nm</td>
<td>Nanometer (wavelength)</td>
</tr>
<tr>
<td>Pa</td>
<td>Pascal</td>
</tr>
<tr>
<td>pc</td>
<td>Postprandial</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell(s), erythrocyte(s)</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>sec</td>
<td>Second, seconds</td>
</tr>
<tr>
<td>Tr</td>
<td>Trace</td>
</tr>
<tr>
<td>U</td>
<td>International unit of enzyme activity</td>
</tr>
<tr>
<td>V</td>
<td>Volume</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell(s)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>wk</td>
<td>Week, weeks</td>
</tr>
<tr>
<td>yr</td>
<td>Year, years</td>
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### Table 727-3
#### Abbreviations for Specimens in Table 727-5

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>S</td>
<td>Serum</td>
</tr>
<tr>
<td>P</td>
<td>Plasma</td>
</tr>
<tr>
<td>(H)</td>
<td>Heparin</td>
</tr>
<tr>
<td>(LiH)</td>
<td>Lithium heparin</td>
</tr>
<tr>
<td>(E)</td>
<td>Ethylenediaminetetraacetic acid (EDTA)</td>
</tr>
<tr>
<td>(C)</td>
<td>Citrate</td>
</tr>
<tr>
<td>(O)</td>
<td>Oxalate</td>
</tr>
<tr>
<td>W</td>
<td>Whole blood</td>
</tr>
<tr>
<td>(NH4H)</td>
<td>Ammonium heparinate</td>
</tr>
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</table>

### Table 727-4
#### Key to Comments Section of Table 727-5

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<th>Comment</th>
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<tbody>
<tr>
<td>30°C, 37°C</td>
<td>Temperature of enzymatic analysis (Celsius)</td>
</tr>
<tr>
<td>a</td>
<td>Values obtained are significantly method dependent</td>
</tr>
<tr>
<td>b</td>
<td>Values in older males are higher than those in older females</td>
</tr>
<tr>
<td>c</td>
<td>Values in older females are higher than those in older males</td>
</tr>
<tr>
<td>d</td>
<td>Atomic absorption</td>
</tr>
<tr>
<td>e</td>
<td>Borate affinity chromatography</td>
</tr>
<tr>
<td>f</td>
<td>Cation-exchange chromatography</td>
</tr>
<tr>
<td>g</td>
<td>Vitros, a proprietary analytic system of Ortho Clinical Diagnostics, Inc.</td>
</tr>
<tr>
<td>i</td>
<td>Electrophoresis</td>
</tr>
<tr>
<td>j</td>
<td>Enzymatic assay</td>
</tr>
<tr>
<td>k</td>
<td>Enzyme-amplified immunoassay</td>
</tr>
<tr>
<td>l</td>
<td>Fluorometric method</td>
</tr>
<tr>
<td>m</td>
<td>Fluorescence-activated cell sorting (FACS)</td>
</tr>
<tr>
<td>n</td>
<td>Fluorescence polarization</td>
</tr>
<tr>
<td>o</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>p</td>
<td>High-performance liquid chromatography (HPLC)</td>
</tr>
<tr>
<td>q</td>
<td>Indirect fluorescence antibody (IFA) assay</td>
</tr>
<tr>
<td>r</td>
<td>Ion-selective electrode</td>
</tr>
<tr>
<td>s</td>
<td>Nephelometry</td>
</tr>
<tr>
<td>t</td>
<td>Optical density</td>
</tr>
<tr>
<td>u</td>
<td>Radial immunodiffusion (RID)</td>
</tr>
<tr>
<td>v</td>
<td>Radioimmunoassay (RIA)</td>
</tr>
<tr>
<td>w</td>
<td>Spectrophotometry</td>
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### Table 727-5
#### Reference Intervals

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<thead>
<tr>
<th>Complete Blood Count</th>
<th>Specimen</th>
<th>Reference Values (US)</th>
<th>Conversion Factor</th>
<th>Reference Values (SI)</th>
<th>Comments</th>
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<tr>
<td>Hematocrit (HCT, Hct)</td>
<td>W(E)</td>
<td>% of packed red cells (V red cells/V whole blood cells x 100)</td>
<td>×0.01</td>
<td>0.44-0.70</td>
<td>MW Hb = 64,500</td>
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<tr>
<td>Calculated from mean corpuscular volume (MCV) and RBC count (electronic displacement or laser)</td>
<td>0-30 days</td>
<td>44-70%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>1-23 mo</td>
<td>32-42%</td>
<td></td>
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<tr>
<td></td>
<td>2-9 yr</td>
<td>33-43%</td>
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<tr>
<td></td>
<td>10-17 yr M</td>
<td>36-47%</td>
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<tr>
<td></td>
<td>F</td>
<td>35-45%</td>
<td></td>
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<tr>
<td></td>
<td>&gt;18-99 yr M</td>
<td>42-52%</td>
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<td>F</td>
<td>37-47%</td>
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<tr>
<td>Hemoglobin (Hb)</td>
<td>W(E)</td>
<td>g/dL</td>
<td>×0.155</td>
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<tr>
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<td>1-23 mo</td>
<td>10.5-14.0</td>
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<tr>
<td></td>
<td>2-9 yr</td>
<td>11.5-14.5</td>
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<tr>
<td></td>
<td>10-17 yr M</td>
<td>12.5-16.1</td>
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<td>F</td>
<td>12.0-15.0</td>
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<td>F</td>
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<td>P(H)</td>
<td>See Chemical Elements</td>
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<th>REFERENCE VALUES (SI)</th>
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<td>Mean corpuscular hemoglobin (MCH)</td>
<td>W(E)</td>
<td>pg/cell</td>
<td>x0.0155</td>
<td>fmol/cell</td>
<td>0.51-0.60</td>
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<td></td>
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<td>33-39</td>
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<td>1-23 mo</td>
<td>24-30</td>
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<td>0.39-0.48</td>
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<td>2-9 yr</td>
<td>25-31</td>
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<td>0.26-0.32</td>
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<tr>
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<td>10-17 yr M</td>
<td>26-32</td>
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<td></td>
<td>0.26-0.32</td>
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<tr>
<td></td>
<td>F &gt;18-99 yr M</td>
<td>27-31</td>
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<td>0.27-0.31</td>
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<tr>
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<td>F</td>
<td>27-31</td>
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<td>0.27-0.31</td>
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<td>Mean corpuscular hemoglobin concentration (MCHC)</td>
<td>W(E)</td>
<td>% Hb/cell or g Hb/dL</td>
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<td>mmol Hb/L RBC</td>
<td>4.96-5.58</td>
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<td>0-30 days</td>
<td>32-36</td>
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<td>72-88</td>
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<td>1-23 mo</td>
<td>32-36</td>
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<td>&gt;18-99 yr</td>
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<td>76-90</td>
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<td>Leukocyte count (WBC count)</td>
<td>W(E)</td>
<td>×1,000 cells/mm³ (µL)</td>
<td>x1</td>
<td>×109 cells/L</td>
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<td></td>
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<tr>
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<td>4.0-12.0</td>
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<td>x0.01</td>
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<td>Neutrophils (&quot;bands&quot;)</td>
<td>3-5%</td>
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<td>Neutrophils (&quot;segs&quot;)</td>
<td>54-62%</td>
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<td>0.54-0.62</td>
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</tr>
<tr>
<td>Lymphocytes</td>
<td>25-33%</td>
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<td>0.25-0.33</td>
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<tr>
<td>Monocytes</td>
<td>3-7%</td>
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<td>0.03-0.07</td>
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<tr>
<td>Eosinophils</td>
<td>1-3%</td>
<td></td>
<td>0.01-0.03</td>
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<tr>
<td>Basophils</td>
<td>0-0.75%</td>
<td></td>
<td>0-0.0075</td>
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</tr>
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<td></td>
<td>Cells/mm³ (µL)</td>
<td>0-250</td>
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<tr>
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<td>×106 cells/L</td>
<td>0.0075</td>
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<tr>
<td>Myelocytes</td>
<td>0%</td>
<td>x1</td>
<td>0</td>
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<tr>
<td>Neutrophils (&quot;bands&quot;)</td>
<td>150-400</td>
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<td>Neutrophils (&quot;segs&quot;)</td>
<td>3,000-5,800</td>
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<td>Eosinophils</td>
<td>15-50</td>
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<td>0.01-0.03</td>
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<td>Basophils</td>
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<td>0.0075</td>
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<td>Platelet count (thrombocyte count)</td>
<td>W(E)</td>
<td>×103/mm³ (µL)</td>
<td>x106</td>
<td>×109/L</td>
<td>84-478</td>
</tr>
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<td></td>
<td>Newborn</td>
<td>84-478 (after 1 wk, same as adult)</td>
<td></td>
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<td>(Buck, 1996)</td>
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<td>Adult</td>
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<td>150-400</td>
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<td>Reticulocyte count</td>
<td>W(E,H,O)</td>
<td>Adults 0.5-1.5% of erythrocytes or 25,000-75,000/mm³ (µL)</td>
<td>x0.01</td>
<td>0.005-0.015 (number fraction) or 25,000-75,000 x 10⁶/L</td>
<td>Number fraction</td>
</tr>
<tr>
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<td>W(cap)</td>
<td>0.4-6.0</td>
<td>x0.01</td>
<td>0.004-0.060</td>
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<tr>
<td></td>
<td>0-30 days</td>
<td>&lt;0.1-1.3</td>
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<td>&lt;0.001-0.013</td>
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<td></td>
<td>1-4 wk</td>
<td>&lt;1.0-1.2</td>
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<td>5-6 wk</td>
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<td>7-8 wk</td>
<td>0.1-2.9</td>
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<td>9-10 wk</td>
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<td>11-12 wk</td>
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### Table 727-5 Reference Intervals—cont’d

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<td>Alanine aminotransferase (ALT, SGPT)</td>
<td>S</td>
<td>0-7 days</td>
<td>6-40 U/L</td>
<td>x1</td>
<td>6-40 U/L</td>
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<tr>
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<td>8-30 days</td>
<td>10-40</td>
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<td>1-12 mo</td>
<td>5-45</td>
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<tr>
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<td>1-19 yr</td>
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<tr>
<td></td>
<td>P</td>
<td>18-30 g/dL</td>
<td>x10</td>
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<td>Albumin (BCG)</td>
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<td>Full term &lt;6 days</td>
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<td>30-100 U/L</td>
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<td>480-800 U</td>
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<td>Aspartate aminotransferase (AST, SGOT)</td>
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<td>10-15 yr</td>
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<td>Base excess</td>
<td>W(H)</td>
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<td>mmol/L</td>
<td>x1</td>
<td>mmol/L</td>
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<td></td>
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<td>Child</td>
<td>(-7)--(-1)</td>
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<td></td>
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<td>Thereafter</td>
<td>(-4)--(+2)</td>
<td></td>
<td>(-4)--(+2)</td>
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<td>(-3)--(+3)</td>
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<td>(-3)--(+3)</td>
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<td>Bicarbonate</td>
<td>S,P</td>
<td>Arterial</td>
<td>21-28</td>
<td>x1</td>
<td>21-28</td>
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<td></td>
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<td>Venous</td>
<td>22-29</td>
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<tr>
<td>Bilirubin, total</td>
<td>S</td>
<td>mg/dL</td>
<td></td>
<td>µmol/L</td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>See Bhutani nomogram (Fig. 727-3)</td>
<td>×17.1</td>
<td></td>
<td>(Bhutani, Johnson, Sivieri, 1999)</td>
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</tr>
<tr>
<td>1 mo-adult</td>
<td>&lt;1.0</td>
<td></td>
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<td>&lt;17</td>
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<tr>
<td>C-reactive protein (high sensitivity)</td>
<td>S</td>
<td>M (mg/dL)</td>
<td>F (mg/dL)</td>
<td>M (mg/L) F (mg/L)</td>
<td>(Soldin, et al, 2004)</td>
</tr>
<tr>
<td>0-90 days</td>
<td>0.08-1.58</td>
<td>0.09-1.58</td>
<td></td>
<td>0.8-15.8 0.9-15.8</td>
<td></td>
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<tr>
<td>91 days-12 mo</td>
<td>0.08-1.12</td>
<td>0.05-0.79</td>
<td></td>
<td>0.8-11.2 0.5-7.9</td>
<td></td>
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<tr>
<td>13 mo-3 yr</td>
<td>0.08-1.12</td>
<td>0.08-0.79</td>
<td></td>
<td>0.8-11.2 0.8-7.9</td>
<td></td>
</tr>
<tr>
<td>4-10 yr</td>
<td>0.06-0.79</td>
<td>0.5-1.0</td>
<td></td>
<td>0.6-7.9 0.5-10.0</td>
<td></td>
</tr>
<tr>
<td>11-14 yr</td>
<td>0.08-0.76</td>
<td>0.06-0.81</td>
<td></td>
<td>0.8-7.6 0.6-8.1</td>
<td></td>
</tr>
<tr>
<td>15-18 yr</td>
<td>0.04-0.79</td>
<td>0.06-0.79</td>
<td></td>
<td>0.4-7.9 0.6-7.9</td>
<td></td>
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<tr>
<td>Calcium, ionized (Ca)</td>
<td>S,P(H),W(H)</td>
<td>mg/dL</td>
<td></td>
<td>mmol/L</td>
<td></td>
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<tr>
<td>Cord blood</td>
<td>5.0-6.0</td>
<td>×0.25</td>
<td></td>
<td>1.25-1.50 1.07-1.27</td>
<td></td>
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<tr>
<td>Newborn, 3-24 hr</td>
<td>4.3-5.1</td>
<td>1.00-1.17</td>
<td></td>
<td></td>
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<tr>
<td>24-48 hr</td>
<td>4.0-4.7</td>
<td>1.12-1.23</td>
<td></td>
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<tr>
<td>Thereafter</td>
<td>4.8-4.92</td>
<td>1.12-1.23</td>
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<td>Calcium, total</td>
<td>S</td>
<td>mg/dL</td>
<td></td>
<td>mmol/L</td>
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<tr>
<td>Cord blood</td>
<td>9.0-11.5</td>
<td>×0.25</td>
<td></td>
<td>2.25-2.88 2.3-2.65</td>
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<tr>
<td>Newborn, 3-24 hr</td>
<td>9.0-10.6</td>
<td>1.75-3.00</td>
<td></td>
<td></td>
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<tr>
<td>24-48 hr</td>
<td>7.0-12.0</td>
<td>2.25-2.73</td>
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<tr>
<td>Thereafter</td>
<td>8.8-10.8</td>
<td>2.20-2.70</td>
<td></td>
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<tr>
<td>Carbon dioxide, partial pressure (pCO₂)</td>
<td>W(H)</td>
<td>mm Hg</td>
<td></td>
<td>kPa</td>
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<tr>
<td>Newborn</td>
<td>27-40</td>
<td>×0.1333</td>
<td></td>
<td>3.6-5.3 3.6-5.5</td>
<td></td>
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<tr>
<td>Infant</td>
<td>27-41</td>
<td>3.6-5.5</td>
<td></td>
<td>4.7-6.4 4.3-6.0</td>
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<tr>
<td>Thereafter M F</td>
<td>35-48</td>
<td>1.75-3.00</td>
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<tr>
<td>Carbon monoxide (carboxyhemoglobin)</td>
<td>W(E)</td>
<td>% HbCO</td>
<td></td>
<td>HbCO fraction &lt;0.02</td>
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<tr>
<td>Nonsmoker</td>
<td>&lt;2%</td>
<td>×0.01</td>
<td></td>
<td>&lt;0.10 &gt;0.5</td>
<td></td>
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<tr>
<td>Smoker</td>
<td>&lt;10%</td>
<td>2.0-2.70</td>
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<td></td>
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<tr>
<td>Lethal</td>
<td>≥50%</td>
<td>2.10-2.55</td>
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<tr>
<td>Chloride</td>
<td>S,P(H)</td>
<td>96-104 mmol/L</td>
<td>x1</td>
<td>96-104 mmol/L 98-106</td>
<td>(Farrell, et al, 2008)</td>
</tr>
<tr>
<td>Chloride, sweat</td>
<td>Sweat</td>
<td>mmol/L</td>
<td></td>
<td>CF unlikely intermediate indicative of CF</td>
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<tr>
<td>0-5 mo</td>
<td>≤29</td>
<td>CF unlikely intermediate indicative of CF</td>
<td></td>
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<tr>
<td>≥6 mo</td>
<td>30-59</td>
<td>CF unlikely intermediate indicative of CF</td>
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<td>≥60</td>
<td>CF unlikely intermediate indicative of CF</td>
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<tr>
<td>Cortisol</td>
<td>S,P(H)</td>
<td>µg/dL</td>
<td>x27.59</td>
<td>nmol/L</td>
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<td>Newborn Adults, 8:00 AM</td>
<td>1-24</td>
<td>28-662</td>
<td></td>
<td>(Jedeikin, et al, 1982)</td>
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<tr>
<td>4:00 PM 8:00 PM</td>
<td>5-23</td>
<td>138-635</td>
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<tr>
<td></td>
<td>3-15</td>
<td>82-413</td>
<td></td>
<td>≤0.50 Fraction of 8:00 AM ≤0.50</td>
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<tr>
<td>Creatine kinase</td>
<td>S</td>
<td>70-380 U/L</td>
<td>x1</td>
<td>70-380 U/L 214-1,175</td>
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<td>5-8 hr</td>
<td>214-1,175</td>
<td>130-1,200</td>
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<tr>
<td>24-33 hr</td>
<td>87-725</td>
<td>130-1,200</td>
<td></td>
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<tr>
<td>72-100 hr Adult</td>
<td>5-130</td>
<td>87-725</td>
<td></td>
<td>5-130</td>
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<tr>
<td>Creatine kinase isoenzymes</td>
<td>S</td>
<td>% MB</td>
<td>% BB</td>
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<td>Creatinine (IDMS)</td>
<td>S,P</td>
<td>0-4 yr</td>
<td>0.03-0.50</td>
<td>×88.4</td>
<td>μmol/L</td>
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<tr>
<td></td>
<td></td>
<td>4-7 yr</td>
<td>0.03-0.59</td>
<td></td>
<td>g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-10 yr</td>
<td>0.22-0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-14 yr</td>
<td>0.31-0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;14 yr</td>
<td>0.50-1.06</td>
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<tr>
<td>Creatinine clearance (endogenous)</td>
<td>S,P,U</td>
<td>Newborn 40-65 mL/min/1.73 m²</td>
<td>&lt;40 yr, M 97-137</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>F 88-128</td>
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<td></td>
<td></td>
<td></td>
<td>Decreases &lt;6.5 mL/min/decade</td>
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<tr>
<td>Ferritin</td>
<td>S</td>
<td>0-6 wk</td>
<td>0.03-0.59</td>
<td>×1</td>
<td>µg/L</td>
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<tr>
<td></td>
<td></td>
<td>7 wk-365 days</td>
<td>0.03-0.59</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1-9 yr</td>
<td>0.03-0.59</td>
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<tr>
<td></td>
<td></td>
<td>10-18 yr M</td>
<td>0.03-0.59</td>
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<tr>
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<td></td>
<td>F</td>
<td>0.03-0.59</td>
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<tr>
<td>Folate</td>
<td>S</td>
<td>Newborn 7.0-32 ng/mL</td>
<td>×2.265</td>
<td></td>
<td>15.9-72.4 nmol/L</td>
</tr>
<tr>
<td></td>
<td>W(E)</td>
<td>Thereafter 1.8-9.0</td>
<td>10-95</td>
<td></td>
<td>4.1-20.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150-450 ng/mL RBCs</td>
<td>10-95</td>
<td></td>
<td>340-1,020 nmol/L cells</td>
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<td>Glucose</td>
<td>S</td>
<td>Cord blood</td>
<td>45-96</td>
<td>×0.0555</td>
<td>mmol/L</td>
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<tr>
<td></td>
<td></td>
<td>Premature</td>
<td>20-60</td>
<td></td>
<td>2.5-5.3</td>
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<tr>
<td></td>
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<td>Neonate</td>
<td>30-60</td>
<td></td>
<td>1.1-3.3</td>
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<td></td>
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<td>Newborn 1 day</td>
<td>40-60</td>
<td></td>
<td>1.7-3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1 day</td>
<td>50-90</td>
<td></td>
<td>2.2-3.3</td>
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<td>Child</td>
<td>60-100</td>
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<td>2.8-5.0</td>
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<td>Adult</td>
<td>70-105</td>
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<td>3.3-5.5</td>
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<td>Adult</td>
<td>65-95</td>
<td></td>
<td>3.9-5.8</td>
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<td>W(H)</td>
<td>Cord blood</td>
<td>&lt;120</td>
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<td>3.6-5.3</td>
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<td>Glucose, 2 hr post</td>
<td>S</td>
<td>10-120</td>
<td>&lt;6.7</td>
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<tr>
<td>Glucose tolerance test (GTT) (see Chapter 589)</td>
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<td>Fasting 70-105</td>
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<td>0.0555</td>
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<td>Oral dose</td>
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<td>Normal 70-120</td>
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<td>Adult: 75 g</td>
<td></td>
<td>Diabetic 126</td>
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<tr>
<td>Child: 1.75 g/kg of ideal weight, up to a maximum of 75 g</td>
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<td>200</td>
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<tr>
<td>Glucose-6-phosphate dehydrogenase (G6PD) in erythrocytes</td>
<td></td>
<td>Normal 3.9-5.8</td>
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<td>Bishop, modified</td>
<td>W(E,H,C)</td>
<td>120 min</td>
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<td>adult</td>
<td></td>
<td>Fasting 70-120</td>
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<tr>
<td>3.4-8.0 U/g Hb</td>
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<td>Normal 70-105</td>
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<td>98.6-232 U/1012 RBC</td>
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<td>Diabetic 126</td>
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<tr>
<td>1.16-2.72 U/mL RBC</td>
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<td>200</td>
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<tr>
<td>Newborn: 50% higher</td>
<td></td>
<td>x10</td>
<td>0.0645</td>
<td>x10-3</td>
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<tr>
<td>37°C, b (Knight and Haymond, 1981)</td>
<td></td>
<td>13-147</td>
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<tr>
<td>12-123</td>
<td></td>
<td>8-90</td>
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<td>5-32</td>
<td></td>
<td>5-24</td>
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<tr>
<td>1.16-2.72 U/mL RBC</td>
<td></td>
<td>5-16</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Newborn: 50% higher</td>
<td></td>
<td>37°C</td>
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<tr>
<td>0.22-0.52 mlU/mmol Hb</td>
<td></td>
<td>37-193</td>
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<tr>
<td>0.10-0.23 mlU/106 RBC</td>
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<td>13-147</td>
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<tr>
<td>1.16-2.72 HU/L RBC</td>
<td></td>
<td>12-123</td>
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<tr>
<td>Immunoglobulin A (IgA)</td>
<td>S</td>
<td>0-1 mo</td>
<td>1.4-3.6</td>
<td>x10</td>
<td>mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 mo</td>
<td>1.3-5.3</td>
<td></td>
<td>14-36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4 mo</td>
<td>4.4-84</td>
<td></td>
<td>13-530</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 mo-10 yr</td>
<td>11-106</td>
<td></td>
<td>44-840</td>
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<tr>
<td></td>
<td></td>
<td>10-15 yr</td>
<td>14-159</td>
<td></td>
<td>110-1,060</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-10 yr</td>
<td>33-236</td>
<td></td>
<td>140-1,590</td>
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<tr>
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<td></td>
<td>Adult</td>
<td>70-312</td>
<td></td>
<td>330-2,360</td>
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<td>6-10 yr</td>
<td>700-3,120</td>
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<th>CONVERSION FACTOR</th>
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<th>COMMENTS</th>
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<tbody>
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<td>Immunoglobulin D (IgD)</td>
<td>S</td>
<td>Newborn: none detected</td>
<td></td>
<td>None detected</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thereafter: 0-8 mg/dL</td>
<td>×10</td>
<td>0-80 mg/L</td>
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</tr>
<tr>
<td>Immunoglobulin E (IgE)</td>
<td>S</td>
<td>M 0-230 IU/mL F 0-170</td>
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<td>0-230 kU/L 0-170</td>
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<tr>
<td>Immunoglobulin G (IgG)</td>
<td>S</td>
<td>Cord blood 1 mo 2-4 mo 5-12 mo 1-5 yr 6-10 yr Adult</td>
<td>mg/dL ×0.01</td>
<td>g/L 3.6-16.06 2.51-9.06 1.76-6.01 1.72-10.69 3.45-12.36 6.08-15.72 6.39-13.49</td>
<td>s (Meites, 1989)</td>
</tr>
<tr>
<td>Immunoglobulin M (IgM)</td>
<td>S</td>
<td>Cord blood 1-4 mo 5-9 mo 10 mo-1 yr 2-8 yr 9-10 yr Adult</td>
<td>mg/dL ×10</td>
<td>mg/L 63-250 170-1,050 330-1,260 410-1,730 430-2,070 520-2,420 560-3,520</td>
<td>s (Meites, 1989)</td>
</tr>
<tr>
<td>Iron</td>
<td>P</td>
<td>All ages</td>
<td>mg/dL ×0.1791</td>
<td>µmol/L 4.33-11.6</td>
<td>(Lockitch, et al, 1988)</td>
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<tr>
<td>Iron-binding capacity, total (TIBC)</td>
<td>S</td>
<td>Infant 100-400 µg/dL Thereafter 250-400</td>
<td>×0.179</td>
<td>17.90-71.60 44.75-71.60</td>
<td>(Lockitch, Halstead, Wadsworth, et al, 1988)</td>
</tr>
<tr>
<td>L-lactate (perchloric acid)</td>
<td>W</td>
<td>1-12 mo 1-7 yr 7-15 yr</td>
<td>mg/dL ×1</td>
<td>mmol/L 1.1-2.3 0.8-1.5 0.6-0.9</td>
<td>(Bonnefont, et al, 1990)</td>
</tr>
<tr>
<td>D-lactate</td>
<td>P(H)</td>
<td>6 mo-3 yr</td>
<td>0.0-0.3</td>
<td>×1</td>
<td>0.0-0.3</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>S</td>
<td>&lt;1 yr 1-9 yr 10-19 yr</td>
<td>U/L ×1</td>
<td>U/L 170-580 150-500 120-330</td>
<td>37°C, a (Meites, 1989)</td>
</tr>
<tr>
<td>Isoenzymes</td>
<td>S</td>
<td>% of total activity 1-6 yr 7-19 yr LD1, 2, 3, 4, 5</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Lead</td>
<td>W(H)</td>
<td>Child Toxic</td>
<td>µg/dL ×0.0483</td>
<td>mmol/L &lt;0.0024 ≥3.38</td>
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<tr>
<td>Lipase</td>
<td>P,S</td>
<td>1-18 yr</td>
<td>145-216 U/L</td>
<td>×1</td>
<td>145-216 U/L</td>
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<tr>
<td>Magnesium</td>
<td>P(H)</td>
<td>0-6 days 7 days-2 yr 2-14 yr 0.78 ± 0.37% of total Hb</td>
<td>mg/dL ×0.411</td>
<td>mmol/L 0.48-1.05 0.65-1.05 0.60-0.95 0.0787 ± 0.0037</td>
<td>w (Meites, 1989)</td>
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<td>Osmolality</td>
<td>S</td>
<td>Child, adult</td>
<td>275-295 mOsm/kg H₂O</td>
<td>275-295 mOsm/kg H₂O</td>
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<tr>
<td>Phosphatase, alkaline</td>
<td>S</td>
<td>1-9 yr 10-11 yr</td>
<td>U/L ×1</td>
<td>U/L 145-420 140-560</td>
<td>37°C, aw</td>
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<td></td>
<td></td>
<td>12-13 yr 14-15 yr 16-19 yr</td>
<td>M</td>
<td>M</td>
<td>200-495 105-420 65-260</td>
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<td></td>
<td>10-11 yr 12-13 yr 14-15 yr 16-19 yr</td>
<td>F</td>
<td>F</td>
<td>105-420 70-230 50-130</td>
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<td>1-9 yr 10-11 yr</td>
<td>F</td>
<td>F</td>
<td>105-420 70-230 50-130</td>
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<td>12-13 yr 14-15 yr 16-19 yr</td>
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<td>200-495 105-420 65-260</td>
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### Table 727-5  Reference Intervals—cont’d

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<th>REFERENCE VALUES (SI)</th>
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<td>Phosphorus, inorganic</td>
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<td>Potassium</td>
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<td>mg/L</td>
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<td>Pyruvate (perchloric acid)</td>
<td>W</td>
<td>0.076 ± 0.026 mmol/L</td>
<td>x1</td>
<td>0.076 ± 0.026 mmol/L</td>
<td>(Pianosi, Seargeant, Haworth, 1995)</td>
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<td>Sodium</td>
<td>S,P (Li,H, NH₄H)</td>
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<td>x1</td>
<td>mmol/L</td>
<td>g (Greely, Snell, Colaco, 1993)</td>
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<td>134-144</td>
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<td>Child</td>
<td>mmol/L</td>
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<tr>
<td>Thereafter</td>
<td>mmol/L</td>
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<td>Thyroid-stimulating hormone</td>
<td>S</td>
<td>µIU/L</td>
<td>x1</td>
<td>µIU/L</td>
<td>g (Dugaw, Jack, Rutledge, 2001)</td>
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<td>0.5-4.5</td>
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<td>0.5-4.5</td>
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<td>Thyroid uptake of radioactive iodine</td>
<td>Activity over thyroid gland</td>
<td>%</td>
<td>x0.01</td>
<td>2 hr &lt;0.06</td>
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<tr>
<td>2 hr</td>
<td>%</td>
<td>≤6%</td>
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<td>2 hr 0.03-0.20</td>
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<td>6 hr</td>
<td>%</td>
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<td>24 hr 0.08-0.30</td>
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<td>24 hr</td>
<td>%</td>
<td>8-30%</td>
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<tr>
<td>Thyroid uptake of technetium-99m</td>
<td>Activity over thyroid gland</td>
<td>%</td>
<td>x0.01</td>
<td>Fractional uptake 0.004-0.030</td>
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<td>After 24 hr</td>
<td>%</td>
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<td>0.004-0.030</td>
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<td>Thyrotropin-releasing hormone (TRH)</td>
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<td>x2.759</td>
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<td>5-60 pg/mL</td>
<td>pg/mL</td>
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<td>Thyroxine-binding globulin (TBG)</td>
<td>S</td>
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<td>x10</td>
<td>mg/L</td>
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<tr>
<td>Cord blood</td>
<td>mg/dL</td>
<td>1.4-9.4</td>
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<td>14-94</td>
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<td>1-4 wk</td>
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<td>mg/dL</td>
<td>2.9-5.4</td>
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<td>Adult</td>
<td>mg/dL</td>
<td>1.5-3.4</td>
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<td>15-34</td>
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<th>CONVERSION FACTOR</th>
<th>REFERENCE VALUES (SI)</th>
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<td>Thyroxine, total</td>
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<td>nmol/L</td>
<td>(Dugaw, Jack, Rutledge, 2001)</td>
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<td>4.5-10.0</td>
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<td>4.5-10.0</td>
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<td>pmol/L</td>
<td>(Dugaw, Jack, Rutledge, 2001)</td>
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<td>pmol/L</td>
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<td>pmol/L</td>
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<td>Urea nitrogen</td>
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<td>mmol/L</td>
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<td>μmol/L</td>
<td>(Lockitch, Halstead, Albersheim, et al, 1988)</td>
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*In preparing the reference range listings, a number of abbreviations, symbols, and codes were used (see Table 727-2). Reference values are shown in SI units (International System of Units) and US units (Traditional Units).*
Figure 727-1 Nomogram for the estimation of surface area. The surface area is indicated where a straight line that connects the height and weight levels intersects the surface area column, or if the patient is roughly of average size, from the weight alone (enclosed area). (Nomogram modified from the data of E. Boyd by C.D. West. See also Briars GL, Bailey BJ: Surface area estimation: pocket calculator v nomogram, Arch Dis Child 70:246–247, 1994.)

Figure 727-2 Relationships among body weight (lb), body surface area, and adult dosage. The surface area values correspond with those set forth by Crawford JD, Terry ME, Rourke GM: Simplification of drug dosage calculation by application of the surface area principle, Pediatrics 5:783–790, 1950. Note that the 100% adult dose is for a patient weighing approximately 140 lb and having a surface area of approximately 1.7 m². (From Talbot NB, Richie RH, Crawford JH: Metabolic homeostasis: a syllabus for those concerned with the care of patients, Cambridge, MA, 1959, Harvard University Press.)

Figure 727-3 Nomogram for risk assessment of hyperbilirubinemia. (From Bhutani VK, Johnson L, Sivieri EM: Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns, Pediatrics 103:6–14, 1999, Fig. 2, p. 9.)